NINTH EDITION

## Self Assessment & Review

# MEDICINE

## Part A


*By*

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*Dedicated to*

*My Parents*

***My thoughts bear an indelible imprint of their vision.***

# Preface

The structure of Postgraduate Entrance Examinations has undergone a dramatic change over past years with the pattern of examinations moving from a *'Paper-based' 'All India Postgraduate Examination'* to a *'Computer-based' NEET.*

While All India Institute of Medical Sciences (AIIMS) conducted the earlier test, National Board of Examinations (NBE) conducts the present examination 'NEET'.

Postgraduate Entrance Examination whether *AIPGME* OR *NEET* remains our battleground and the dates of the battle has already been decided!

**Five long years have been long enough time for each one of us to realize our potential strengths and weaknesses. Nevertheless, this year is qualitatively unlike the past, for it carries with it, an invisible force of strength, unprecedented energy and firmness of purpose like never before. As if our latent capacities were lying in a state of inactivity, only to reemerge and domineer over our weakness and distractions.**

**Our vigor, durability, toughness is all put to test but the vehemence to succeed or the fear of failure drives us on. As if we reinvented the essence of the golden words**

*'When the going gets tough the tough, gets going'*

FRIENDS !

**It would certainly be an understatement, if I say that it is strategy that sees you through in this most bewildering examination rather than the genius in you or the amount of core knowledge that you possess.**

**The most brilliant of students you have always feared and envied are often left dismayed, surprised, and shocked at their performance results, while the most average ones have been seen to become the ideals of those setting their first foot forward into this blind race.**

**Most of us and you too must have wondered.**

What is it after all... that turned this average guy into a marvelous performer?

**FIRST is the** 'will to succeed' **flanked by** courage, faith **and** confidence **in your own vision.**

*'If you have the will to win, you have achieved half your success;*

*If you don't, you have achieved half your failures.'* — *David Ambrose*

**Never dismiss the possibility of success as a distant dream or a matter of chance. Eliminate all tendencies to take a gloomy or cynical view of affairs. Always choose to take a look at the better side of things. Keep your mind 'solution-focused' rather than 'problem-focused'.**

*'What the caterpillar calls the end of the world, the master calls a butterfly'*

**SECOND** is effort, persistence and determination; NO QUITTING

**There is certainly no route to success in a PG entrance examination without the cornerstone of exhausting relentless effort that leaves you thoroughly worn out.**

*'Destiny is not a matter of chance, it is a matter of choice;*

*It is not a thing to be waited for, it is a thing to be achieved'* —*Williams Jennings Bryan*

**The route to success is difficult and long and often just before every big achievement, every great accomplishment, comes anxiety with a fear of failure and discouragement.**

**Persistence—that is the key, and you must hold on, with the faith that your resolution and firmness would generate sufficient amount of energy to help you sail past this one year.**

*'Stick to the fight when you are hardest hit, it's when things go wrong that you must not quit.'*

**THIRD** and foremost is Strategy!

**Strategy is the distinction between knowledge and wisdom.**

**Analysis and maximum revelation out of the same raw stock in our grey matter is what sets those who perform apart from those who fail to perform with an equal effort. While friends effort provides the foundation without which the tomb of your success would never build, it is strategy, that sets your structure apart from those of others.**

What then should be your strategy?

**In the simplest words the answer to the above question lies in the following line:**

*Try and know all what has been asked previously, the most recent questions being the most important.*

All the best!

***Mudit Khanna***

Dear Friends,

The structure of Postgraduate Entrance Examinations has undergone a dramatic change over past year with the pattern of examinations moving from a *'Paper-based' 'All India Postgraduate Examination'* to a *'Computer-based' NEET.*

While All India Institute of Medical Sciences (AIIMS) conducted the earlier test, National Board of Examinations (NBE) conducts the present examination 'NEET'. This has not only brought about a change in the preparatory content but also a change to the best approach to the same content.

To help you prepare for the test in a more efficient manner we have made certain key changes in the format of the book.

1. We have edited the content in the book to provide *Essential Revision Notes* before each chapter. This will allow the student to revise all relevant and important 'key' topics much quicker and in a more structured and coordinated manner. In the present edition we have not deleted content from the explanatory answers primarily to allow the reader, to choose an 'Antegrade' approach (First read the Essential Revision Notes-Theory and then attempt answering the questions) or a 'Retrograde' approach (First attempt answering the questions with detailed explanatory answers, and then revise the theory from the Essential Revision Notes-Theory section in the book).

2. We have included the latest years DNB Questions to broaden the relevant question bank besides the latest questions from All India Post Graduate Medical Examinations (AIPGME) and the All India Institute of Medical Sciences (AIIMS) Examinations.

We understand that this approach has led to repetition of content within the same book, but the objective for the same has been to make it relatively easy for the reader to understand and integrate the content in a more efficient manner. We are open to suggestions and would welcome and appreciate any suggestions to improve the book further, by deleting or adding further content as desired.

**Mudit Khanna**

# Acknowledgments

***'To Dear God, whose eternal blessings and divine presence helps us to fulfill all our goals'.***

When emotions are profound, words sometimes are not sufficient to express our thanks and gratitude. I express my sincere thanks to all people who have helped and provided consistent enthusiasm and encouragement in bringing out this work.

I would like to take this opportunity to offer my special thanks to Mr Habil Khorakiwala, Ms Zahabiya Khorakiwala, Mr Arvind Baganiya and the entire family of Wockhardt Group of Hospitals for their constant inspiration and support right from the time, I joined the department of Orthopedics at Wockhardt Hospital, Goa.

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Expressions and emotions fail to find words to express thanks to my parents. I thank them for being a constant source of inspiration and motivation. Their confidence in me has always propelled me to work harder.

My wife, Diksha and daughter, Vanya—words are hard to find, when it comes to highlighting their role, in the making of this book. I thank them for always standing by my side.

I express my special thanks to all my friends, especially Dr Anurag Shukla, Dr Yogesh Chaudhuri, Dr Sachin Jadhav, Dr Minal Jadhav, Dr Saurabh Agarwal, Dr Gunjan, Dr Chitwan, Dr Ashish Gupta and Dr Amit Tripathi for their presence and support at all times.

Special thanks to Shri Jitendar P Vij (Group Chairman) of Jaypee Brothers Medical Publishers (P) Ltd, New Delhi, India for his inspiring guidance and suggestions that helped me a lot in accomplishing this huge task.

Sincere thanks are also extended to Mr Sayeed and Mr Saleem and M/s Compsphere for their technical help and layout design. Their committed effort in presenting this work on paper is deeply appreciated.

I am highly grateful to the readers of the previous editions for their creative criticism, overwhelming response, immediate acceptance of the overall contents of the book and for their queries and suggestions.

The last but not the least, I gratefully acknowledge and thank in anticipation, all readers who, I am confident, will act and continue to act as a guiding torch in improving and upgrading the content of this book.

Friends your feedback and suggestions are always welcome at *muditkhanna@yahoo.com*

*From the Publisher's Desk*

We request all the readers to provide us their valuable suggestions/errors (if any) *at:*

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so as to help us in further improvement of this book in the subsequent edition.

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***

# Hematology

## ESSENTIAL REVISION NOTES

# Classification of Anemia

## Morphological Classification of Anemia

| MCV (Mean Corpuscular Volume) | MCHC (Mean Corpuscular Hb concentration) |
|---|---|
| • Mean Corpuscular Volume refers to the average size of the RBC (volume).<br>• MCV is usually expressed in femtoilitres (fl)<br>• Normal MCV varies from 79.0 to 93.3 fl *(H 18th/3587)*<br>Raised MCV: *Macrocytic*<br>Normal MCV: *Normocytic*<br>Reduced MCV: *Microcytic* | • Mean Corpuscular Haemoglobin Concentration (MCHC) refers to the average concentration of Hb in the RBC (MCHC describes the colour of the RBC)<br>• MCHC is usually expressed in pg/dl<br>• Normal MCHC varies from 32.3 to 35.9 pg/dl *(H 18th/3587)*<br>Raised MCHC: *Hyperchromic*<br>Normal MCHC: *Normochromic*<br>Reduced MCHC: *Hypochromic* |

## Morphological Classification of Anemia based on MCV and MCHC

**Morphological classification of Anemia**

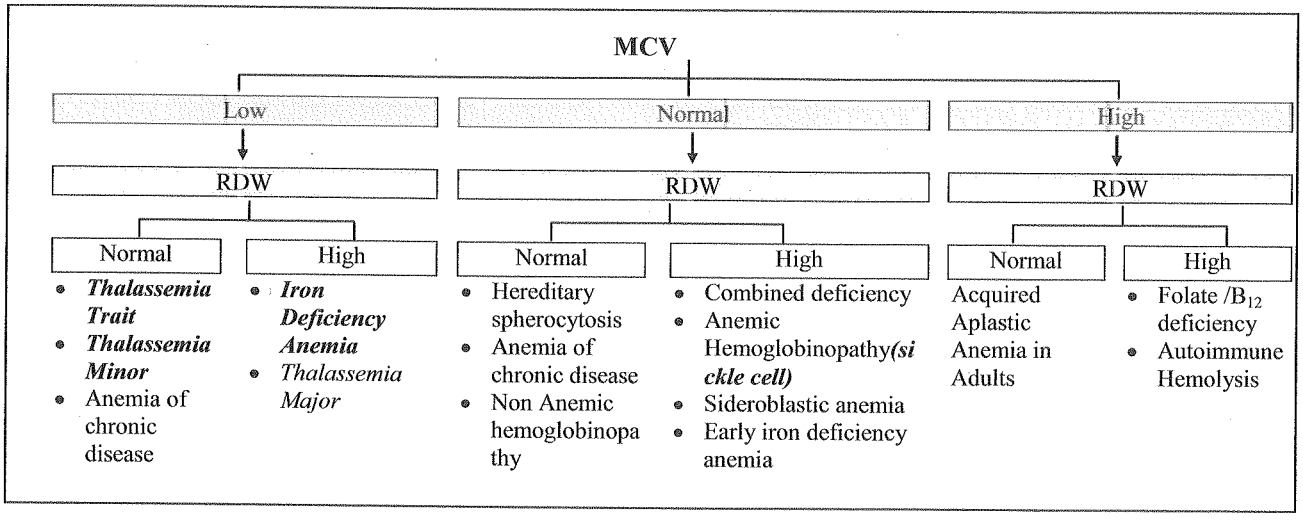
- **Microcytic (Low MCV) Hypochromic (Lew MCHC)**
  - ***Iron deficiency***
  - ***Thalassemia***
  - ***Sideroblastic anemia***
  - Lead toxicity
  - (+/-) Anemia of chronic disease
- **Normocytic (Normal MCV) Normochromic (Normal MCHC)**
  - High Reticulocyte Count
    - Hemangioma
    - DIC
    - Hemolytic anemia
      - Intrinsic RBC defects
        - RBC membrane disorder
          - Hereditary spherocytosis
          - Hereditary elliptocytosis
        - RBC enzyme disorders
          - G6PD deficiency
          - Pyruvate kinase deficiency
      - Extrinsic RBC defects
        - HUS
        - Autoimmune
        - Alloimune
    - Sickle cell anemia
    - Blood loss
  - Low Reticulocyte Count
    - Red cell aplasia
      - TEC
      - *Diamond Blackfan syndrome*
      - *Parvovirus B19 infection*$^{Q}$
    - Malignancy
    - Fanconi anemia
    - *Anemia of chronic disease*
    - *Anemia of renal disease*
- **Macrocytic (Raised MCV) Normochromic (Normal MCHC)**
  - ***Vitamin B12 deficiency***
  - Thiamine deficiency
  - ***Folate deficiency***

Most of the anemias mentioned in this section have a normal MCV & MCHC.
However, Macrocytic (↑MCV) or Microcytic (↓MCV) and Hypochromic (↓MCHC) cases may all be encountered

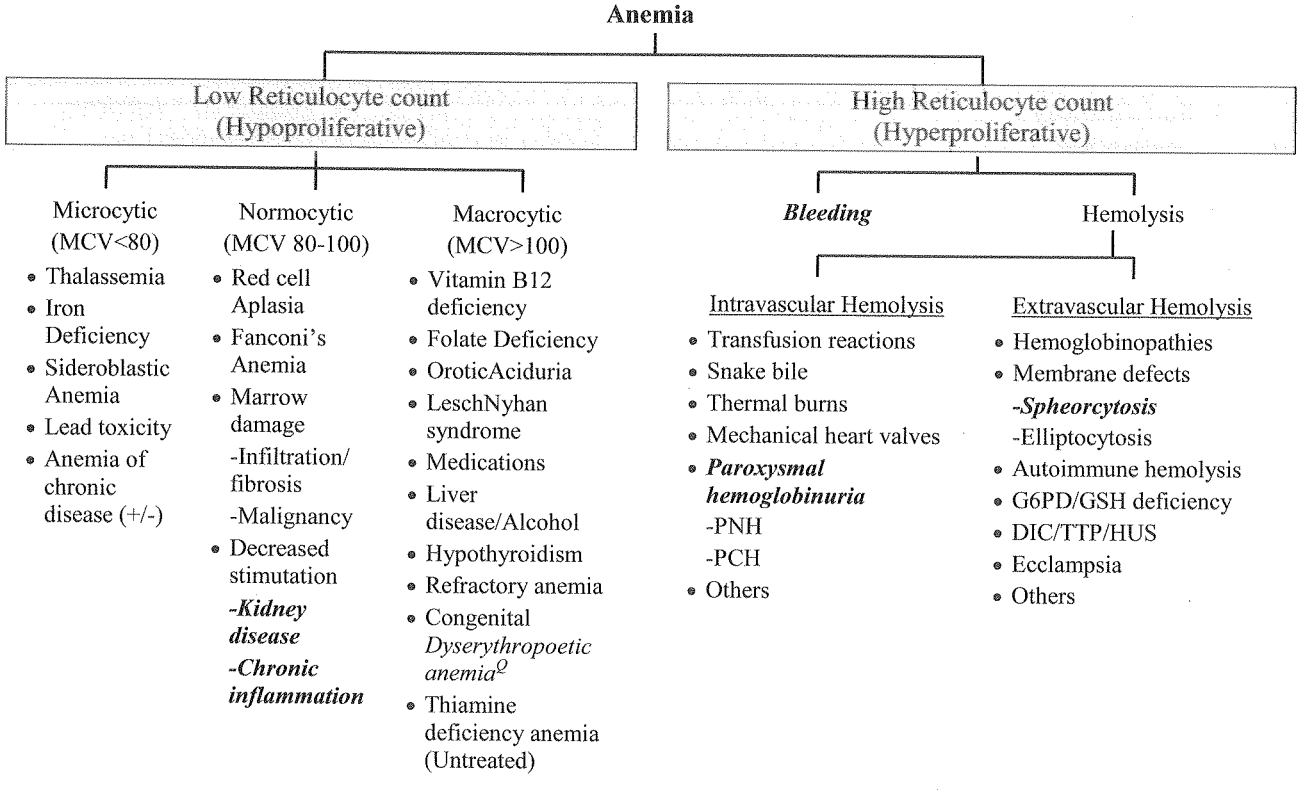
Macrocytic Anemia is characterized by an increase in the MCV The Haemoglobin content increases proportionately to the erythrocyticvoume.
***Therefore as a rule macrocytic anemia is normochromic.***

**Anemia of chronic disease may present with microcytic hypochromic anemia*
*Anemia of chronic disease: Normocytic Normochromic > Microcytic Hypochromic*

## Classification of Anemia based on MCV and Red Cell Distribution Width (RDW)




## Classification of Anemia based on Reticulocyte Count



# Hypochromic Microcytic Anemias

## Causes of Microcytic hypochromic Anemia

**Causes of microcytic hypochromic anaemia**

- *Iron deficiency anaemia*
- *Thalassemia*
- *Sideroblasticanaemia*
- *Lead poisoning*
- *Anemia of chronic disease (+/-)*

## Differential Diagnosis of Microcytic Hypochromic Anemia

| Condition / Test (normal values) | Iron deficiency | Thalassemia | Sideroblastic anemia | Anemia of chronic disease |
|---|---|---|---|---|
| **Smear** | Microcytic hypochromic | Microcytic hypochromic | Microcytic hypochromic | Normocytic normochromic > Micro/hypochromic (but Micro/Hypo may be present) |
| **Serum iron (50-150µg/dl)** | Low (<30) | Normal | Normal | ↓ (<50) |
| **TIBC (300-600 µg/dl)** | High (>360) | Normal | Normal (Chandrasoma Taylor) | ↓ (<300) |
| **% Saturation (30-50%)** | < 10 (↓ed) | N or ↑ed (30-80) | N or ↑ (30-80) | ↓ (10-20) |
| **Ferritin (µg/l) (50-200 µg/L)** | < 15 (↓ed) | ↑ (50-300) | ↑ (50-300) | Normal or ↑ (30-200) |
| **Hemoglobin pattern** | Normal | Abnormal | Normal | Normal |
| **Free Erythrocyte Protporphrin** | ↑ed | Normal | ↑ed | ↑ed |
| **RDW** | ↑ed | Normal | Normal | Normal |

**Microcytic Hypochromic Anemias are typically associated with a Normal or High Red Cell Distribution Width and normal or High Free Erythrocyte Protoporphyrin**

***Microcytic Hypochromic anemias are not associated with Low Red Cell Distribution Width and Low Free Erythrocyte Protoporphyrin***

*Hypochromic microcytic anemia with ↓serum iron and ↑TIBC: iron Deficiency Anemia*

*Hypochromic microcytic anemia with ↓ serum iron and ↓TIBC : Anemia of Chronic disease*

# Causes of Macrocytic Anemias

**Causes of Macrocytic anemia**

1. *Vit. $B_{12}$ deficiency*
2. *Folic acid deficiency*
3. *Oroticaciduria*
4. *Nitrous oxide inhalation*
5. *Liver disease*
6. *Hypothyroidism*
7. *Thiamine deficiency*

# Hemolysis and Hemolytic Anemias

## Intravascular Hemolysis vs Extravascular Hemolysis

**Hemolysis**

*Increased destruction of RBC's (Anemia)*[Q]
*Increased compensatory Erythropoesis (↑ed Reticulocytes)* [Q]

← *Serum LDH Levels are increased*[Q]

### Intravascular Hemolysis

RBC's are degraded intravascularly within the plasma

***Free haemoglobin in plasma***[Q]

**Haptogobin pathway**

Free Hb binds Haptaglobin present in the plasma to form a complex

↓

Hb-Haptaglobin complex is rapidly cleared by the liver

***Plasma Haptaglobin levels are Decreased***[Q]

**Methemoglobin pathway**

After saturating haptoglobin Some remaining Hb is oxidized to methemoglobin

*↑Methemoglobin*

Methamoglobin in plasma may be excreated directly by the kidney

*Methemoglobinuria*[Q] immediately after intravascular hemolysis

Methemoglobin in plasma may dissociated and bind albumin to form methemalbumin

*Methemalbumin*[Q] persists in plasma for about 24 hours and is cleared by hepatocytes.

**Haemoglobin/ Haemosidirin Pathway**

Remaining free Hb is excreted from the kidney either as free haemoglobin or hemosiderin

*Hemoglobinuria*(immediately after intravascular hemolysis)
*Hemosidinuria*(Several days after intravascular hemolysis)

### Extravascular Hemolysis

RBC's are degraded within the cells of the Raticuloendothelial system (spleen, liver)

*Splenomegaly*[Q] *is seen*

Haemoglobin is degraded within the RES

Haem → Iron

*Iron* is conserved and *deposited within the bone marrow*[Q]

Globin → Bilirubin

*Increasedunconjugated bilirubin levels*[Q]

↓

*Increased urinary urobilinogen*[Q]
*Increased fecal stereobilinogen*[Q]

***Note***

*Although decreased haptaglobin levels are more characteristic of intravascular hemolysis, decreased levels are also seen in cases of extravascular hemolysis. This is because even in Extravascular hemolysis, enough haemoglobin levels leaks out of the macrophages to bind with and deplete haptaglobin*

## Laboratory Evaluation of Haemolysis

| | Extravascular | Intravascular |
|---|---|---|
| **Hematologic** | | |
| Routine blood film | Polychromatophilia | Polychromatophilia |
| Reticulocyte count | ↑ | ↑ |
| Bone marrow examination | Erythroid hyperplasia | Erythroid hyperplasia |
| **Plasma or serum** | | |
| Bilirubin | ↑ Unconjugated | ↑ Unconjugated |
| Haptoglobin | ↓ | Absent |
| Plasma hemoglobin | N - ↑ | ↑↑ |
| Lactate dehydrogenase | ↑ (Variable) | ↑↑ (Variable) |
| **Urine** | | |
| Bilirubin | 0 | 0 |
| Hemosiderin | 0 | + |
| Hemoglobin | 0 | + in severe cases |

## Intravascular Hemolysis vs Extravascular Hemolysis

### Intravascular Hemolysis vs Extravascular Hemolysis

**Causes of intravascular hemolysis**

- Blood transfusion
  - ***ABO mismatched transfusion***
  - Infected blood
- *Thermal burns*
- *Snake bites*
- *Sepsis*
  - Bacterial / parasitic infections
  - Clostridial sepsis
  - Malaria
  - Bartonellosis
  - *Mycoplasma pneumoniae*
- *Mechanical heart valves*
- ***Paroxysmal hemoglobinuria***
  - PNH
  - PCH

**Causes of extravascular hemolysis**

- Blood and viral infections
  - Malaria
  - *Mycoplasma pneumoiae*
  - Infectious mononucleosis
- Drug-induced hemolysis
  - G6PD/GSH deficiency
  - Autoimmune drug reactions
  - Strong oxidant drugs/chemicals
- Autoimmune hemolysis
  - Warm-reacting (IgG) AIHA
  - Cold-reacting (IgM) AIHA
- Hemoglobinopathies
  - ***Thalassemia***
- Membrane structural defect
  - Hereditary sperocytosis
  - Hereditary spherocytosis
  - Acanthocytosis
- Environmental disorders
  - Malignancy/DIC
  - TTP/HUS
  - Eclampsia or Preeclampsia

## Characteristic features of Hemolytic Anemia:

| Increased red cell breakdown | Compensatory increase red cell production |
|---|---|
| • *↓Hemoglobin (Anemia)* | • *Reticulocyte **count is** ↑ed Q* |
| • Serum bilirubin is ↑ed *(Unconjugated bilirubin ↑ed)Q* | • *Routine blood film shows a variety of abnormal morphological types of red cells Q*<br>- *Schistocytes*<br>- ***Spherocytes**Q etc.* |
| • *Urine urobilinogen is ↑edQ* | • *Bone narrow*↑ MCV / ↑ MCH (The increased number of reticulocytes is associated with an increased MCV) |
| • *Fecal stercobilinogen is ↑edQ* | • Macrocytes, Polychromasia& sometimes nucleated red cells in smear |
| • *Hemoglobinemia / Hemoglobinuria Q* | • *Shows erythroid hyperplasia with raised iron stores. Q* |
| • *Methemoglobinemia Q* | • *X Rays of bones show:*<br>- ***Evidence** of expansion of marrow space, especially in tubular bones & in skull Q*<br>- ***Bossing** of skull Q* |
| • ***↓ Haptoglobin Hemoglobin binding proteins Q such as Haptoglobin and Hemopexin are reduced or absent. Q*** | |
| • ***Hemosiderinuria Q*** | |
| • *Plasma Lactic dehydrogenase Q (LDH) is ↑ed* | |
| • *↑ AST* | |

**Both intravascular and extravascular hemolysis are characterized by elevated reticulocyte counts**

| High Reticulocyte count<br>Reticulcyte production index >2.5 |
|---|

# Hereditary Spherocytosis

*HS is characterised by defect in one of the proteins in the cytoskeleton of Red cell membrane, leading to loss of membrane, and hence* ***decreased ratio of surface area to volume*** *and consequently spherocytosis.*

- ***Hereditary spherocytosis is inherited as an Autosomal Dominant Trait*** $^{Q}$
- ***Most common membrane defect is that of Ankyrin***

**Proteins that may be defective in Hereditarysphenocytosis**

*Protein Defects causing Hereditary Spherocytosis: Ankyrin> Protein 3 ≥Spectrin>Palladin*

| Proteins that may be defective in Hereditarysphenocytosis | | |
|---|---|---|
| • ***Ankyrin:*** *(Most common defect)* $^{Q}$ | : | (Defective in about 50% of cases) |
| • ***Protein 3:(Anion transport channel)*** | : | (Defective in about 25% of cases) |
| • ***Spectrin:*** (Spectrin or αspectrin) | : | (Defective in most of remaining 25% of cases) |
| • ***Palladin:****(Protein 4.2)* $^{Q}$ | : | (Rare defect, but may cause H. S) |

- ***One characteristic clinical presentation is Striking splenomegaly*** $^{Q}$ ***(Anemia, Splenomegaly and Jaundice)***
- ***One characteristic Laboratory abnormality in HS is 'Increased Osmotic Fragility'***

| Characteristic Laboratory abnormalities |
|---|
| • *The mean corpuscular volume (MCV) : is decreased* $^{Q}$ |
| • *The mean corpuscular Hb. concentration (MCHC) : is increased* $^{Q}$ |
| • *Osmotic fragility is : increased* $^{Q}$ |

**Osmotic Fragility**

Osmotic fragility of red cells is defined as the ease with which red cells are ruptured (hemolysed) when they are exposed to hypotonic solution.
Osmotic fragility test assesses the integrity of the membrane of red cells.

**Increased Osmotic Fragility**

Cells which have a lower surface to volume ratio such as spherocytes from any cause have increased osmotic fragility

Conditions

- ***Hereditary spherocytosis (HS)***
- Autoimmune Hemolytic Anemias (AIHA)
- Hemolytic Disease of new born
- Malaria
- Severe pyruvate kinase deficiency
- Other conditions in which spherocytes are found in the blood

**Decreased Osmotic Fragility**

Cells which have a high surface to volume ratio such as thin/hypochromic/target cells have decreased osmotic fragility.

- ***Thalassemia*** *(otherhemoglobinopathieseg. HbC, HbS)*
- *Iron deficiency anemia*
- ***Sickle cell anemia***
- *Post splenectomy*
- *Reticulocytosis*
- *Other conditions in which thin/target cells are found in the blood.*

- ***Treatment of Choice for Hereditary Spherocytosis is 'Splenectomy'*** $^{Q}$

# Sickle Cell Disease/Anemia

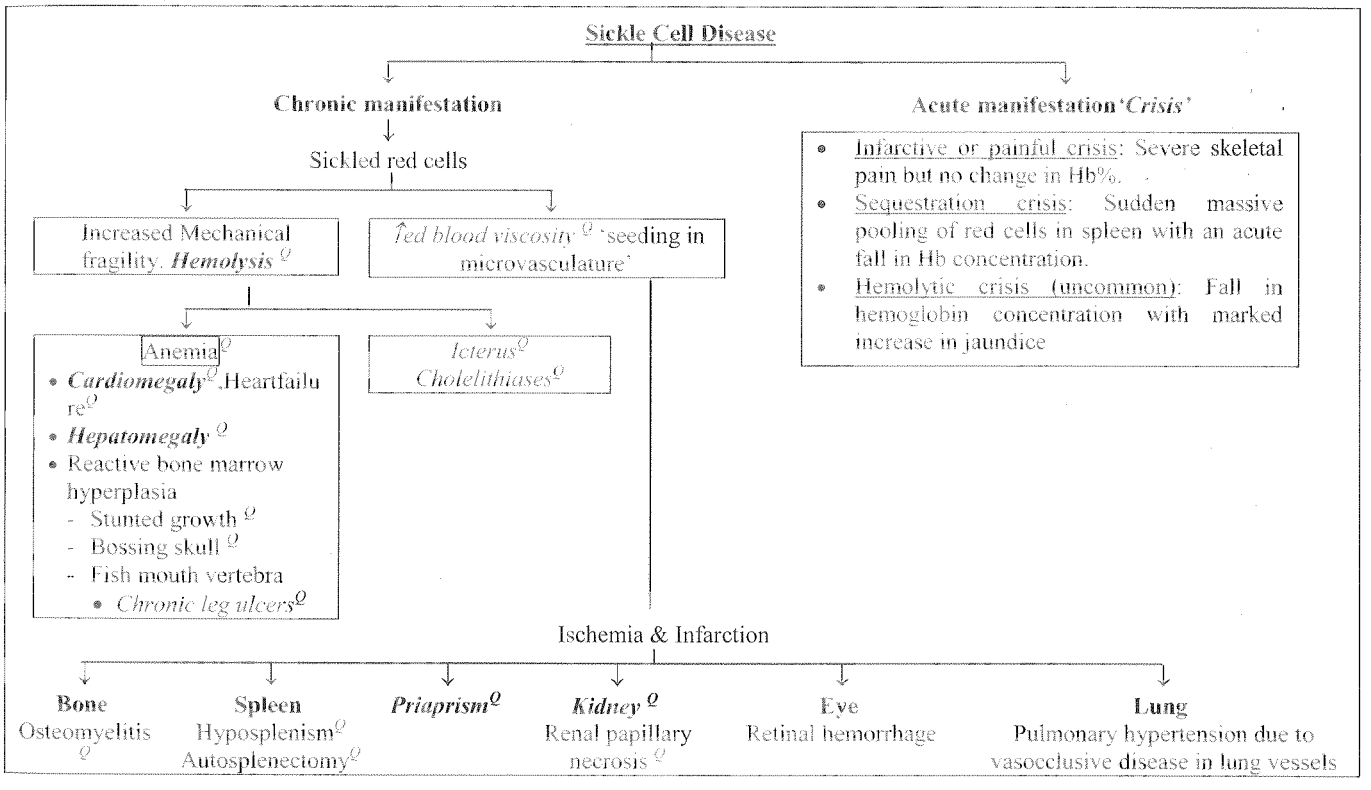
***Sickle Cell Anemia is characterized by increased number of 'Sickled' red blood cells in the circulation. These sickled cells are more fragile (increased mechanical fragility: hemolysis) than normal red blood cells and tend to increase the viscosity of blood (ischemia and infarction)***

## Mutation causing Sickle Cell Disease:

***The sickle cell anemia is caused by a mutation in the beta globin gene that changes the sixth amino acid from glutamic acid to valine in the beta chain of HbA ($\alpha_2\beta_2$).***

| Designation | Mutation |
|---|---|
| HbS (Sickle) ($\beta^{6Glu} \rightarrow$ Val) | Replacement of Glutamate by Valine at position 6 beta chain of HbA |
| HbC ($\beta^{6Glu} \rightarrow$ Lys) | Replacement of Glutamate by Lysine at position 6 on beta chain of HbA |
| HbE ($\beta^{26Glu} \rightarrow$Lys) | Replacement of Glutamate by Lysine at position 26 on beta chain of HbA |

## Clinical Manifestations of Sickle Cell Disease:



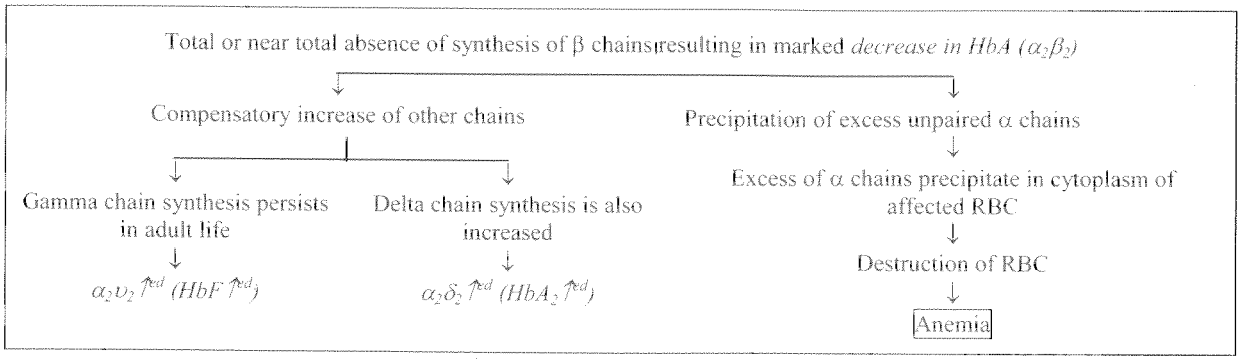

## Factors favouring Sickling Crisis:

**Factors favouring polymerization:** Q

1. **Hypoxia** Q : (2,3 diphosphoglycerate increases polymerization Q)
2. **Acidosis** Q : decreased pH enhances polymerization Q
3. **Haemoglobin** concentration Q: Higher concentration leads to increased polymerization Q
4. **Combination of HbS with other haemoglobins**: This depends on the extent of homology with other haemoglobins. Descending order of ability to copolymerization are HbS, C, D, O, Arab, A, J & F ***(Least with HbF)***

# Thalassemias

- Thalassemias are characterized by *decreased rate of synthesis of Hb chains* [Q] that are *structurally normal* [Q]




- *β-thalassemia or Cooley's anemia is the commonest thalassemia*
- Most types of Beta thalassemia are caused by point mutations affecting one or few bases.
- The ***most common site of mutations in Beta thalassemia is the intervening sequence 1 (IVS-1) or Intron 1***

## Alpha and Beta Thalassemia Traits:

**Thalassemia Trait**

| Alpha Thalassemia Trait | Beta thalassemia trait (T. minor) |
|---|---|
| • *Normal $HBA_2$*<br>• *Normal HBF*<br>• Mild Anemia<br>- Mild Microcytosis<br>- Mild Hypochromia<br>• No need for Blood transfusion | • ↑ *$HBA_2$*<br>• ↑ *HBF*<br>• Mild Anemia<br>- Mild Microcytosis<br>- Mild Hypochromia<br>• No need for blood transfusion |

## Causes of CREW-CUT Appearance (Hair on End Appearance):

Crew cut appearance (Hair on End appearance)

- Thalassemia (Most charachteristic)
- Sickle cell Anemia (2nd most characteristic)
- Other Hemolytic anamias (May be seen)

## Clinical spectrum of Thalassemia (β thalassemia):

| Syndrome | Thalassemia major (Serious homozygos form) | Thalassemia intermedia (They are also homozygos) | Thalassemia minor (heterozygos form) |
|---|---|---|---|
| General characteristic | • Presentation in early infancy with:<br>- Progressive pallor<br>- Hepatosplenomegaly<br>- Bony changes<br>• Invariably fatal during first few years of life if left untreated (Require repeated blood transfusions) | • Patient present somewhere between the two extremes with variable clinical manifestations of<br>- Progressive pallor<br>- Hepatosplenomegaly<br>- Bony changes<br>• These patients maintain hemoglobin levels between 6-10 g/dl and lead their life fairly comfortably. These patients may need occasional transfusions but are not dependent on blood transfusions for their survival. | • Presents late and patient can lead a practically normal life except for mild persistent anemia<br>• These patients are not dependent on blood transfusions |

| Clinical Features | | | |
|---|---|---|---|
| • Severity of disease | ++++ | ++ | ± |
| • Growth and development | Impaired | - | - |
| • Splenomegaly | ++++ | ++ | - |
| • Jaundice | ++ | +/- | - |
| • Skeletal changes | +++ | + | - |
| • Thalassemia facies | +++ | + | - |
| **Haematological findings** | | | |
| • Anaemia Hb gm/dl | < 7 (severe) | 7-10 (moderate) | >10 |
| • Microcytosis | +++ | ++ | + |
| • Hypochromia | +++ | ++ | + |
| • Basophilic stippling | ++ | + | + |
| • Anisopoikilocytosis | +++ | ++ | ± |
| • Target cells | +++ | ++ | + |
| • Nucleated red cells | +++ | +/- occasional | - |
| • Reticulocytes | 2-15 | 2-10 | < 5 |
| • HbF | 30-90% | 20-100% | 0-5% |
| • $HbA_2$ | <3.5% | <3.5% | 3.5-8% |
| • B.M. Iron | ++++ | ++ | ± |
| • Iron overload | + | - | - |
| • Life expectancy | 20-28 YEARS | Normal | Normal |

## Autoimmune Hemolytic Anemias

### Classification of Autoimmune Hemolytic Anemias

*Depending upon reactivity of autoantibodies these are divided into two types*

| *Warm antibody hemolytic anemia* | *Cold antibody hemolytic anemia* |
|---|---|
| Antibodies here react at room temperature and are mainly of IgG type ♀ | Antibodies here react better at temperatures lower than 37°C, and are mainly IgM ♀ [An exception is cold reactive antibodies of IgG ♀ type in Paroxysmal cold hemoglobulinuria] ♀ |
| *Causes :* | *Causes :* |
| 1. Idiopathic<br>2. Lymphomas : CLL ♀, Non-Hodgkins, etc.<br>3. SLE ♀ and other Collagen Vascular Diseases ♀<br>4. Drugs : e.g. α Methyldopa ♀ | 1. Acute : Mycoplasma Infection ♀ Infectious mononucleosis ♀<br>2. Chronic : idiopathic ♀<br>3. Paroxysmal cold hemoglobinuria ♀ |
| *Mechanism of Hemolysis :* | *Mechanism of Hemolysis :* |
| Human red cells cooled with IgG are trapped by splenic macrophages - Red cell destruction | Antibodies of IgM type bind on Red cell surface and cause agglutination. Hemolytic effect is mediated through fixation of C3 to RBC surface. ♀ |
| *Diagnosis :* | *Diagnosis :* |
| Positive direct Coomb's test, at 37°C for presence of warm antibodies on surface of Red cell. ♀<br>Positive Indirect Coomb's test at 37°C for presence of large quantities of warm antibodies in serum. ♀ | Positive direct Coomb's test for detection of C3 on the red cell surface, but IgM responsible for coating on red cells is not found. ♀ |

# Microangiopathic Hemolytic Anemias

## Classification and/or causes of Microangiopathic Hemolytic Anemias:

**Classification of Microangiopathic Hemolytic Anemia**

**Primary**

- **Thrombotic thrombocytopenic purpura**
- **Hemolytic uremic syndrome**

**Secondary**

- **Associated with disseminated intravascular coagulation**
  - Infections (sepsis)
  - Shiga-type toxins
  - HIV
  - Snake venoms
  - Abruptio placentae
- **Associated with hypertension**
  - Malignant hypertension
  - Preclampsia, eclampsia,
  - HELLP syndrome
- **Associated with malignancy**
  - Adenocarcinomas; gastrointestinal, breast, lung
- **Associated with drugs and/or radiation**
  - Antineoplastic agents
  - Radiation nephritis and chemotherapy in organ transplantation
  - Ticlopidine
- **Associated with immunologic disorders/Vasculitis**
  - Acute glomerulonephritis
  - SLE
  - Polyarteritisnodosa
  - Scleroderma
  - Other vasculitis
- **Associated with congenital malformations**
  - Cavernous hemangioma (Kasabach-Meritt syndrome)
  - Hemangioendothelioma of the liver
- **Associated with antiphospholipid syndrome** (*NMS Medicine*)
- **Associated with Prosthetic valves** (*Harrison/CMDT*) (Pathologically Macroangiopathic – *Rubin's Pathology*)

**Important causes of Microangiopathic Hemolytic Anemias**

- *TTP*
- *HUS*
- *DIC*
- *Vasculitis (Collagen Vascular Disorders)*
- *Malignant Hypertension/Eclampsia/**HELLP***
- *Disseminated carcinomatosis (Metastasis)*
- *Drugs / Radiation*
- *Antiphospholipidsyndrome(NMS Medicine)*
- *Prosthetic Heart Valve*

(PathologicallyMacroangiopathic – *Rubin's*)

***Patients with microangiopathic hemolytic anemias are usually thrombocytopenic***

*(due to consumption of Platelets).*

## Evan's syndrome (combination of ITP and Autoimmune Hemolytic Anemia (AIHA))

- *Evan's Syndrome refers to a combination of Idiopathic Thrombocytopenic Purpura (ITP) and Autoimmune Hemolytic Anemia (AIHA) in the absence of an underlying cause / disease.*
- The occurence of thrombocytopenia may coincide with episodes of hemolysis or may arise as separate episodes.
- Evan's syndrome is more common in children
- Evan's syndrome tends to be resistanct to management of Warm AIHA or ITP
- ***Evans syndrome presents with 'Thrombocytopenia' and 'Immune Hemolysis'.***

***Evan's syndrome does not present with microangiopathic features or fragmented RBCs.***

# PNH: Paroxysmal Nuctunalhaemoglobinuria

**PNH** is an Acquired[Q] Intracarpuscular[Q] disorder, acquired at stem cell level[Q] by loss characterised by undue sensitivity of red blood cell's membrane to complement[Q]

**Common manifestations:** PNH : Three common manifestation

| **Hemolytic Anemia** | **Venous Thrombosis** | **Deficient Hematopoesis** |
|---|---|---|
| | | Probably due to defect at stem cell level |
| Because of increased activation of complement and complement mediated destruction | Activation of complement indirectly stimulates platelet aggregation and hypercoagulability (thus thrombosis despite thrombocytopenia) | Pancytopenia/Aplastic anemia-H16[th]/ 618<br>- ↓ Granulocytes<br>- Thrombocytes (thrombocytopenia) |
| *Hemoglobinemia*[Q]<br>*Hemoglobinuria*[Q]<br>*Hemosiderinuria*[Q]<br>***Elevated LDH***[Q] | | |

**Why is it called Paroxysmal Nocturnal haemoglobinuria?**

**Basis** :*Acidification enhances activity of complement*

During night when one sleeps **(noctunal)** → Relative Hypoxia → Acidosis → Enhanced complement activity

↓

**Paroxysm** of **Haemoglobinuria** identified by passage of brown urine in morning. ← Complement mediated destruction of red blood cells

Red Cell Membrane is **deficient in two factors** which result in increased activation of complement

1. **DAF**[Q] : Decay accelerating factor that activates decay of complements
2. MIRL CD 59 : inhibits membrane attack complex

## Conditions associated with decreased and increased Leukocyte Alkaline Phosphatase Scores (LAP Score)

| Conditions with decreased LAP scores | Conditions with increased LAP scores |
|---|---|
| 1. P.N.H.[Q] | 1. Polycythemia[Q] |
| 2. C.M.L.[Q] | 2. Leukemoid reaction[Q] |
| | 3. Infection[Q] |

# Aplastic Anemia and Myelodysplastic Syndrome

## Differential diagnosis of Pancytopenia

| Pancytopenia with Hypocellular Bone Marrow |
|---|
| Acquired aplastic anemia |
| Constitutional aplastic anemia |
| (Fanconi's anemia, dyskeratosiscongenita) |
| Some myelodysplastic syndromes |
| Rare aleukemic leukemia (AML) |
| Some acute lymphoid leukemia |
| Some lymphomas of bone marrow |

| Hypocellular bone marrow ±Cytopenia |
|---|
| Q fever |
| Legionnaires' disease |
| Anorexia nervosa, starvation |
| Mycobacteria |

| Pancytopenia with Cellular Bone Marrow | |
|---|---|
| *Primary bone marrow diseases* | *Secondary to systemic diseases* |
| *Myelodysplasia syndromes* | Systemic lupus erythematosus |
| ***Paroxysmal nocturnal hemoglobinuria*** | Hypersplenism |
| *Myelofibrosis* | ***$B_{12}$, folate deficiency (Megaloblastic Anemia)*** |
| Some aleukemic leukemia | Overwhelming infection |
| Myelophthisis | Alcohol |
| Bone marrow lymphoma | Brucellosis |
| Hairy cell leukemia | Sarcoidosis |
| | Tuberculosis |
| | Leishmaniasis |

# Fanconi's Anemia:

**Fanconi's Anemia (F A)**

- *Autosomal Recessive*[Q]
- *Positive Family History*[Q]
- Inherited *chromosomal instability syndrome*[Q]
- The diagnosis of FA is based on the demonstration of increased chromosomal breakage in the presence of DNA cross- linking agents such as mitomycin C (MMC) or Diepoxybutane (DEB)

**Progressive Bone Marrow Failure**

- ***Pancytopenia with hypocellular marrow***
- *Aplastic Anemia* ***(Normochromic-Normocytic)*** *(May be Normochromic Macrocytic)*

***Congenital Anomalies***

- Skeletal
  Short stature
  Radial ray anomalies (thumbs, hands, radii)
  Hip and spine anomalies
- Skin
  Hyperpigmentation (café au lait spots)
  Hypopigmentation
- Genitourinary
  Renal structural anomalies
  Hypogonadism
- Craniofacial
  Microcephaly
  Ophthalmic anomalies (microphthalmia, epicanthal folds)
  Otic anomalies (external and middle ear anomalies, deafness)
- Gastrointestinal malformations
  Esophageal atresia or tracheoesophageal fistula
  Imperforate anus
- Cardiac malformations

**Increased Risk of Malignancy**

- *Fanconi's anemia is a premalignant state.*
- Patents with FA are at increased risk of developing Myelodysplasia (MDS) or *Acute Myeloid Leukemia (AML)*[Q]
- Patients with FA are at increased risk of developing *solid tumours*[Q] particularly squammous cell carcinoma of the head and neck, skin, GIT & genital tract

# Sideroblastic Anemia

## What are Sideroblasts

Sideroblasts are Erythroblasts (Red blood cell precursors) that contain iron (ferritin) granules in their cytoplasm. The iron in these cells is normally located in the cytoplasm away from the nucleus (and stains positive for prussian blue).

In normal bone marrow sideroblasts constitute 20- 40% (approx $1/3^{rd}$) of red blood cell precursors

## What are Ringed Sideroblasts

Ringed sideroblasts are abnormal sideroblasts seen in conditions with disturbed haem synthesis. In these cells iron accumulates within the mitochondria, surrounds the nucleus and does not progress into haemoglobin

Ringed sideroblasts are defined as Nucleated Red blood cells (Erythroblasts) containing five or more granules and encircling at least two – thirds of the nucleus.

Ring sidroblasts are pathological and their presence suggests a diagnosis of sideroblastic anemia whether congenital or acquired

## What are the conditions associated with Ringed Sideroblasts

***Ringed Sideroblasts may be seen in all causes of sideroblatic anemia whether Congenital or Acquired but are most often associated with Myelodysplastic syndromes***

Causes of Sideroblastic Anemia (Ringed Sideroblasts in Bone Marrow)

1. Hereditary Sideroblastic Anemia
2. Acquired Sideroblastic Anemia
   - Primary (Acquired) SideroblasticAnemia***(Myelodysplastic Syndromes)***
   - Secondary (Acquired) SidroblasticAnemia : Secondary to
   - Alcohol (Alcohol induced sidroblasticanemia)$^{Q}$
   - Lead (Lead induced sideroblasticanemia)$^{Q}$
   - Zinc (Zinc induced sidroblasticanemia)$^{Q}$
   - Drugs such as INH, pyrizinamide, cycloserine, chloramphenical etc.
   - Other Myeloprolifirative disorders and Myelofibrosis
3. Others (Rare)
   - Thiamine responsive megaloblastic anemia
   - Pearson's syndrome
   - Hypothermia
   - Certain Haemoglobinopathies

# Myeloproliferative disorders

## Differential Diagnosis of Myeloproliferative disorders

**Myeloproliferative disorders classically include:**

- Polycythemia vera[Q]
- Idiopathic myelofibrosis[Q]
- Essential thrombocytosis[Q]
- Chronic myeloid leukemia[Q]

| Condition | WBCount | Hematocrit/Red cell mass | Platelet count | Red cell morphology |
|---|---|---|---|---|
| CML | ↑↑ | N | N or ↑ | N |
| Myelofibrosis | N or ↓or ↑ | N or ↓ | ↓or N or ↑ | Abnormal |
| Polycythemia | N or ↑ | ↑ | N or ↑ | N |
| Essential Thrombocytosis | N or ↑ | N | ↑↑ | N |

# Polycythemia Vera
## Neoplasm arising in multipotent elements

**Increased Turnover of RBC, Leucocytes, platelets** → *Hyperuricemia*[Q]

### ↑Erythroid elements

**Clinical Features**

These result from Erythrocytosis (polycythemia) and increased blood viscocity

- *Patients are plethoric or cyanotic*
- *Neurological symptoms* [Q]
  - *vertigo, tinnitus*
  - *headache*
  - *dizziness*
  - *visual disturbance*
    *Dimness or vision/ from blockade of retinal vessels*
- *Systolic Hypertension* [Q]
- *Splenomegaly*

**Laboratory features**

- *Increased red cell count*
- *Increased hemoglobin*
- *Increased hematocrit*
- *MCV, MCH and MCHC are normal or low*
- *↑ blood viscosity*
- *↓ ESR (ESR is reduced)* [Q]

### ↑ Granulocyte elements

**Clinical Features**

These result from ↑ Basophils and increased secretion of Histamine

- *Intense pruritis*
- *Peptic ulceration*

**Laboratory features**

- *Mild to moderate leucocytosis (↑ TLC )*
- *Neutrophils are normal*
- *↑ Leukocyte alkaline phosphatase (LAP)* [Q]
- *↑ Transcobalamine I and III*
- *↑ Vitamin B12 binding capacity* [Q]

*Neutrophils are essentially normal and hence there is no increased predisposition for infections*

### ↑ Megakaryocytic elements

**Clinical Features**

These result from increased Platelets and / or platelet functional abnormalities
(Increase risk of both thrombosis and bleeding)

**↑ Platelets (Along with hyperviscocity)** → **↑ Thrombosis**

- *Deep viens thrombosis*
- *Hepatic vein thrombosis*
- *Budd chiari syndrome*
- *Portal and mesenteric venous thrombosis*
- *Myocardial infarction*
- *Stroke*
- *Digital ischemia*

**Abnormal platelet function** → **↑ Bleeding**

- *Upper GI bleeding from bleeding peptic ulcer (most common site of bleeding)*

**Laboratory features**

- *Increased platelet count*
- *Platelet functional abnormalities( Inupio 80% patients)*
- *Abnormal platelet aggregation studies.*

## Various major and minor criteria used for the diagnosis of polycythemia vera in various classification systems

*(WHO criteria (revised and old )/ Polycythemia vera study group criteria)*

| Major | Minor |
|---|---|
| • ***JAK2 V617F mutation*** | • ***Thrombocytosis*** *(> 400 × $10^9$/L)* |
| • *Hemoglobin >18.5 g/dL in men, 16.5 g/dL in women* | • ***Leucocytosis*** *(WBC > 12 × $10^9$/L)* |
| • *Increased red blood cell mass* | • ***Increased leukocyte alkaline phosphatase*** *(LAP > 100U)* |
| • *Splenomegaly* | • *Increased serum B12/binders (B12 > 900 pg/ml; unbound B12 binding capacity > 2200 pg/ml)* |
| • *Clonal genetic abnormality other than Philadelphia chromosome or BCR/ABL in marrow* | • *Low serum erythroprotein levels.* |
| • *Endogenous erythroid colony formation in vitro* | • *Panmyelosis with prominent erythoid and megakaryocytic hyperplasia on bone marrow biopsy.* |
| • *Normal arterial O2 saturation (>92%)* | |

## Revised WHO criteria (Proposed) for the diagnosis of Polycythemia vera

**Revised WHO criteria (Proposed) for the diagnosis of Polycythemia vera**

**Major Criteria**

- Hemoglobin > 18.5 g/dl in men, > 16.5 g/dl in women or evidenced on increased red cell volume
- ***Presence of JAK2 mutation***

**Minor Criteria**

- Hypercellular bone marrow biopsy with panmyelosis with prominent erythroid, granulocytic, and megakaryocytic hyperplasia
- Low serum erythropoietin level
- Endogenous erythroid colony formation in vitro.

## WHO Criteria for the diagnosis of Plycythemia Vera (Prior to the proposed new criterion)

**WHO Criteria*(Previous)* for the diagnosis of Plycythemiavera**

**Major Criteria**

- Red blood cell mas > 25% above mean normal predicted value, or Hb > 18.5 g/dl in men, 16.5 g/dl in women.
- Splenomegaly on palpation
- Clonal genetic abnormality other than Philadelphia chromosome or BCR/ABL in marrow.
- Endogenous erythroid colony formation in vitro

**Minor Criteria**

- Thrombocytosis > 400 × $10^9$/L
- WBC > 12 × $10^9$/L
- Panmyelosis with prominent erythroid and megakaryocytic hyperplasia on bone marrow biopsy.
- Low serum erythropoietin levels.

## Tumors associated with Polycythemia Vera

**Tumors associated with polycythemia veraare:**

- Hypernephroma
- Hepatoma
- Adrenal adenoma
- Pheochromocytoma
- ***Cerebellar Haemangioblastoma***
- Uterine fibromyoma
- Meningioma

## Myelofibrosis

***Extensive fibrosis of bone marrow as part of myelofibrotic / proliferative disorder***

*Unsuccessful ♀ aspiration of bone marrow – **Dry Tap***

**Ineffective erythropoiesis in bone marrow**

- *Leukoerythroblastic♀ picture*
  - Immature Leucocytes
  - Immature RBC's (nucleated)
- *Abnormal large platelets ♀ (dysplastic megakaryocytes)*

**Compensatory haematopoesis at extramedullary sites ♀**

***Tear drop♀*** poikilocytes (red blood cells produced at these abnormal sites are often have abnormal and variable shapes)

***Spleen is enlarged ♀*** (as it is the principal site of extramedullaryhaematopoesis.)

**Most characteristic are the Laboratory findings and the *triad of*♀**

a. Tear drop poikilocytes♀
b. Leukoerythroblastic blood i.e. immature leukocytes and nucleated (immature) RBC's ♀
c. Giant abnormal platelets ♀

*Biopsy of bone marrow to detect reticular or collagen fibrosis is essential for diagnosis.* ♀

## Essential thrombocytosis

**(essentialthrombocythaemia; idiopathic thrombocytosis; hemorrhagic thrombocythaemia)**

Essential thrombocytosis is a myeloproliferative disorder characterized by overproduction of platelets without a definable cause.

| **Clinical features** | **Laboratory Diagnostic features** |
|---|---|
| Symptoms<br>• Haemorrhagictendencies : Easy bruising ♀<br>• Thrombotic tendencies :Microvascular occlusions<br>- Erythromelalgia<br>- Migraine (headache)<br>- Transient ischemic attacks<br>Signs<br>• Splenomegaly : usually mild/moderate *massive splenomegaly is more characteristic of other myeloproliferative disorders.* | • Elevated platelet count is hallmark (often >1000×$10^3$/ μL)<br>• Haematocrit and RBC morphology normal<br>• WBC count is mildly elevated/normal (mildneutrophillicleucocytosis)<br>• LAP is normal or elevated<br>• Philadelphia chromosome is absent |
| **Management in a symptomatic patient** | **Management in symptomatic patient** |
| Elevated platelet count in asymptomatic patient<br>• No therapy is recommended because agents used in treatment place the patient at risk of developing acute leukemia<br>↓<br>Therapy with risk of acute leukemia<br>• Radioactive phosphorus<br>• Hydroxyuria<br>• Alkylating agents | Elevated platelet count in symptomatic patients<br>• Symptoms must be clearly identified to be a consequence of elevated platelet count<br>↓<br>Platelet reduction<br>• IFN a<br>• Anagrelide<br>• Hydroxyurea: *should be considered only if the above agents are not effective or tolerable*<br>*.- Harrison* |

## Lymphomas and Chronic Leukemias

### Hodgkin's Disease/ Lymphoma

**Hodgkin's Disease**

| Classical Hodgkin's Disease | Histogenetically distinct subtype of HodgkinsDisease |
|---|---|
| Variants/Subtypes | Variant/Subtype |
| *Mixed cellularity*<br>*Nodular sclerosis*<br>*Lymphocyte Rich*<br>*Lymphocyte Depletion* | *Lymphocyte predominant*<br>*(Nodular Lymphocyte Predominant)* |
| Characterized by: | Characterized by |
| • *Frequent Reed sternberg cells*<br>• *Characteristic immunophenotype*<br>*CD 15 positive; CD 30 positive*<br>*CD 45 Negative* | • *Rare Reed Sternberg cells*<br>(Frequent Lymphocytic and Histocytic variants (Popcorn cells))<br>• Characteristically different immunophenotype<br>*CD 15 Negative : CD 30 Negative*<br>*CD 45 Positive* |

*Characteristic R.S cells are less frequent in nodular sclerosis variant of Hodgkins but these cells are characteristically positive for CD 15 and CD 30 and negative for CD 45*

**The Hodgkin's lymphomas may be classified into four subtypes according to the Rye's classification.**

*Hodgkins lymphoma subtypes in order of frequency*

1. *Nodular sclerosis (30-60%)*
2. *Mixed cellularity (20-40%)*
3. *Lymphocyte predominance (< 10%)*
4. *Lymphocyte depleted (< 10%)*

***The most common subtype of Hodgkin's Lymphoma is 'Nodular Sclerosis'***

***Incidence: NS > MC > LP > LD***

*Note: WHO classification recognizes another subtype of Hodgkins called 'Lymphocyte Rich' subtype*

**Prognosis of Hodgkin's Lymphoma Variants:**

| Variant | 5 years survival |
|---|---|
| *Lymphocyte predominance* | *90%* |
| *Nodular sclerosis* | *70%* |
| *Mixed cellularity* | *50%* |
| *Lymphocyte depletion* | *40%* |

***Lymphocyte predominant type of Hodgkins lymphoma is associated with the best prognosis.***

Prognosis: LP > NS > MC > LD

**Variants of Reed Sternberg cells:**

**Variants of Reed Sternberg cells**

| Lacunar variant | Mononuclear variant | Lymphohistiocytic variant (Popcorn cell; L and H cells) |
|---|---|---|
| R.S cells variant with a folded or multilobate nuclei and abundant pale cytoplasm which gives the appearance of a nucleus silting in an empty hole (lacunae) on histological sections | R.S cell variant with a single round or oblong nucleus | R.S cell variant with multiple folded or convoluted nuclear contour resembling a popcorn kernel (popcorn cell variant) |
| Characteristically seen in<br>*Nodular Sclerosis subtype* | Characteristically seen in<br>*Mixed cellularity subtype*<br>*Lymphocyte Rich Subtype* | Characteristically seen in<br>*Lymphocyte predominance variant* |

**Remember one Reed Sternberg Variant and one characteristic of each variety**

| Hodgkins lymphoma subtypes | Red Sternberg cells variant | Charachterisitic feature |
|---|---|---|
| *Nodular sclerosis* | Lacunar cells [Q] | *M.C. type (all over the world)* [Q] |
| *Mixed cellularity* | Mononuclear variant[Q] | *M.C. type in India* [Q] |
| *Lymphocyte predominance* | Popcorn cell [Q] (Lymphocytic variant) | *Best prognosis* [Q] |
| *Lymphocyte depleted* | Reticular variant (more cellular) | *Worst prognosis* [Q] |

| Hodgkins Lymphoma | Immunopheno type | Association with EBV | Read Sternberg Cell variant[Q] |
|---|---|---|---|
| Nodular Sclerosis | **CD15 +, CD30 +** | EBV – Ve[Q] | Lacunar cells[Q] (Occasional R-S-cells) |
| Mixed cellularity | **CD15 +, CD30 +** | EBV + Ve[Q] (70%) | Classic Reed Sternberg cells[Q] |
| Lymphocyte depletion | **CD15 +, CD30 +** | EBV +Ve[Q] | Reticular variant[Q] (Frequent R-S cells) |
| Lymphocyte Predominance | CD15 –ve, CD30-ve CD20 +ve, CD45+ve ($H17^{th}$) | EBV – Ve[Q] | Popcorn cell variant[Q] |

**Prognostic Factors In Hodgkin's Lymphoma:**

**Prognostic factors in Hodgkins lymphoma**

| Poor prognostic factors for advanced disease | Poor prognostic factors in Localized disease |
|---|---|
| • Male Gender<br>• Age>45 years<br>• Stage IV Disease<br>• Serum Haemoglobin < 10g<br>• Serum Albumin < 4 g<br>• WBC count > 15,000/$mm^3$<br>• Absolute lymphocyte count <600$mm^3$ | • Male Gender<br>• Age >50 years<br>Histological subtype (mixed cellularity and lymphocyte Depletion)<br>• Elevated ESR<br>• Mediastinal mass >1/3 of thoracic diameter (Mediastinal/thorax ratio > 35%)<br>• Number of involved sites with the same side of diaphragm > 4<br>• Presence of systemic symptoms ('B' symptoms) |
| *These factor predict relapse of advanced disease* | *These factors predict prognosis in patients with clinical stages I and II in Hodgkin's disease.* |

## Treatment of Hodgkin's Lymphoma:

**Treatment of Hodgkin's Lymphoma**

| Classical Hodgkin's Lymphoma | | Nodular Lymhocyte predominant Hodgkin's Lymphoma | |
|---|---|---|---|
| Limited Stage Disease (Favourable/unfavourable) (Stage I, II) | Advanced Disease Stage III, IV | Limited Stage Disease Stage I, II | Advanced Disease Stage III, IV |
| Combined Modality treatment with Radiotherapy and chemotherapy is the treatment of choice<br>Limited Stage Disease (I, II) is primarily managed by a combination of chemotherapy (CT) and Radiotherapy (RT) (CT→RT) | Chemotherapy is the treatment of choice<br>Advanced stage disease is primarily managed by chemotherapy<br>Radiotherapy may be used in advanced disease for bulky disease or residual disease after chemotherapy (PTO) | Radiotherapy alone is the treatment of choice (Involved Field RT or Regional RT may be used)<br>*Some clinicians favour no treatment and merely close follow up* | Chemotherapy is the treatment of choice<br>Advanced stage disease is primarily managed chemotherapy<br>*RT may be used in advanced disease for palliation only and in selected cases after chemotherapy.* |
| CT + RT | CT ( ± RT ) | RT | CT (± RT) |

# Non-Hodgkin's Lymphoma

## Classification of Non-Hodgkin's Lymphoma:

| Classification of Non Hodgkin Lymphoma | |
|---|---|
| **B cell Neoplasms** | **T cell Neoplasms** |
| Neoplasms of immature B cells | Neoplasms of immature T cells |
| Precursor B cell Acute Lymphoblastic leukaemia / lymphoma | Precursor T-cell Acute Lymphoblastic leukaemia / Lymphoma |
| Neoplasms of mature B cells | Neoplasms of mature T cells / NK cells |
| • ***Burkitt'slymphoma***$^{Q}$<br>• ***Hairy cell leukemia***$^{Q}$<br>• ***Mantle cell lymphoma***$^{Q}$<br>• Solitary plasmacytoma / Multiple Myeloma$^{Q}$<br>• Small lymphocytic lymphoma / Chronic lymphocytic leukaemia (CLL)<br>• Follicular lymphoma<br>• Diffuse large B cell lymphoma<br>• Extranodal marginal zone lymphoma (MALT Type) | • Mycosis fungoides : Cutaneous T cell lymphoma<br>• Adult T cell lymphoma / Leukemia<br>• Anaplastic Large T cell / Null cell Lymphoma<br>• Peripheral T cell Lymphoma<br>  ○ Angioimmunoblastic Lymphoma<br>  ○ ***Angiocentric Lymphoma***(Extra-nodal T/NK cell Lymphoma<br>  ○ Enteropathy type intestinal lymphoma<br>  ○ Hepatosplenic lymphoma<br>  ○ Subcutaneous Panniculitis - like lymphoma<br>• T cell granular lymphocytic lymphoma |

# Burkitt's Lymphoma

**Translocations in Burkitt's Lymphoma**

Burkitt's lymphoma / leukemias are associated with reciprocal translocations involving the ***c-myc gene on chromosome 8***

| Most common Translocation (70% cases) | Less common translocations |
|---|---|
| ***t (8; 14):*** c- myc gene on chromosome 8 and IgHheavy chain on chromosome 14 | **t (8; 22)** c- myc gene on chromosome 8 and λ-light chain on chromosome 22<br>**t (2; 8) :** c- myc gene on chromosome 8 and κ-light chain on chromosome -2 |

## Hairy cell leukemia:

Hairy cell leukemia is a rare but distinctive form of chronic B cell leukemia that derives its name from the appearance of fine 'hair like projections'[Q] on the leukaemic cells (large B cells)

| | |
|---|---|
| • **Characteristic cytochemical feature:** | Presence of tartrate resistant acid phosphatase 'TRAP' [Q] in neoplastic B cells |
| • **Cellular features/ Markers**[Q] | • Hairy cells express the pan B cell markers CD 19 and CD 20 and monocyte associated antigen CD 11<br>• Plasma cell associated antigen (PCA-1) is also present – Robbins<br>• Expression of **CD 25**, IL2 and specific adhesion molecules – Harrison 14th/695 |
| • **Clinical features**<br>result largely from infiltration of bone marrow liver and spleen | • Present predominantly in the older age group > 40 years[Q]<br>• Massive splenomegaly[Q] (hepatomegaly is less common)<br>• Lymphadenopathy<br>• Pancytopenia[Q]<br>• Recurrent infections |
| • **Treatment**[Q] | • Current treatment of choice is with purine analogues – Cladribine[Q]<br>• Other drugs used<br>- Pentostotin[Q]<br>- Interferon α[Q]<br>• Splenectomy used to be the standard treatment earlier |

## Mantle cell lymphoma

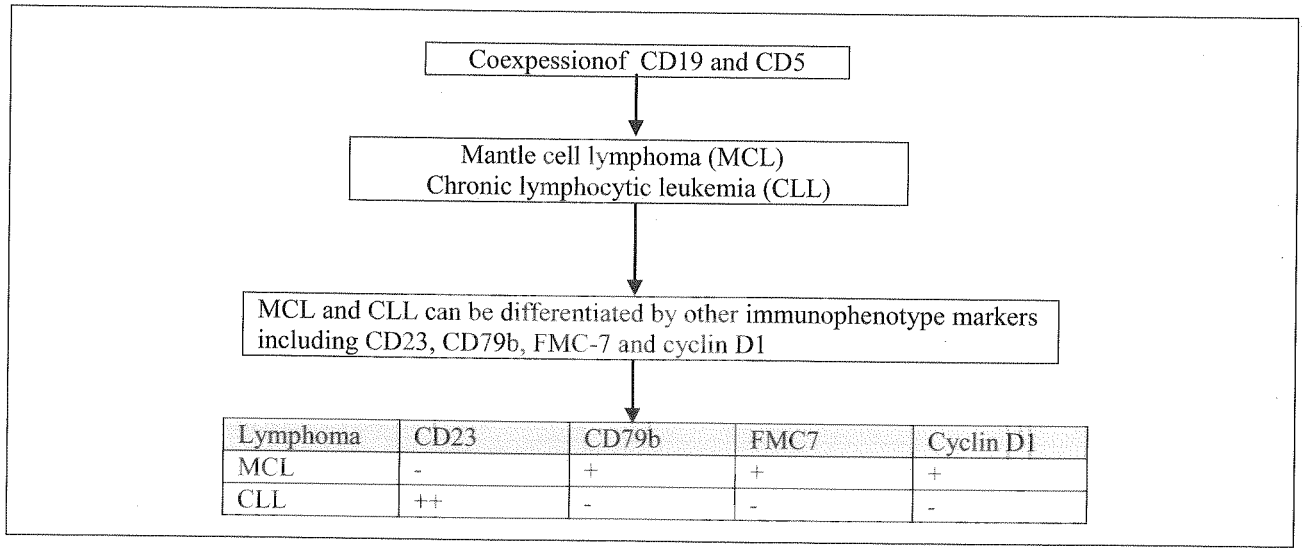
*Presents in the middle aged and the elderly* (Mean Age = 63 yrs– *Harrison 16th/ 648*).

| Clinical profile |
|---|
| - Painless lymphadenopathy<br>- Splenomegaly<br>- Occasional GI involvement |

**Immunocytochemical profile of Mantle Cell Lymphoma**

| CD markers | SURFACE immunoglobulins | Translocation |
|---|---|---|
| • Cells are positive for PAN B markers D 19, CD 2, CD 22, CD 24<br>• Cells are positive for CD 5<br>• Cells are negative for CD 23<br>• Cells are negative for CD 10 | • Moderately high levels of surface immunoglobulins heavy chains IgM &IgD<br>• B cells present bright K positivity (either K or λ light chain may be present) | t (11; 14) translocation 14 t (11; 14) translocation leads to increased expression of cyclin D1 |

**Coexpression of CD19 and CD5 suggests a diagnosis of Mantle Cell Lymphoma or CLL:**




| Lymphoma | CD23 | CD79b | FMC7 | Cyclin D1 |
|---|---|---|---|---|
| MCL | - | + | + | + |
| CLL | ++ | - | - | - |

# Chronic Lymphocytic Leukemia

## Chronic Lymphocytic Leukemia (CLL)

*Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) is tumor composed of monomorphic small B lymphocytes in the peripheral blood, bone marrow and lymphoid organs (spleen and lymph nodes).*

WHO considers both CLL and SLL as a single entity with different presentations. Small lymphocytic lymphoma (SLL) is considered as a tissue equivalent of chronic lymphocytic leukemia (CLL). The CLL/SLL tumor cells coexpress CD5 and CD23.

### Pripheral blood picture

- **Peripheral smear**
  - **RBCs:** Show normocytic normochromic anemia or rarely hemolytic blood picture.
  - **WBCs:** Total leukocyte count is increased and varies from 20-50 x 109/L.

    **Differential Leukocyte Count:**

    *Lymphocytosis* is the characteristic feature and absolute lymphocyte count should be more than 5 x 109/L. *Usually absolute lymphocyte count above 10 x 109/L is common at the time of diagnosis.*

    Lymphocytes constitute more than 50% of the white cells and may reach up to 90-98% with resultant neutropenia (lymphocytes 70-98% and polymorphs 2-30%).

    *Smudge cells*: Smudge cells or basket cells are disintegrated lymphocytes and represent the spread out nuclear material observed in the peripheral blood film. They are due to rupture of the neoplastic lymphoid cells while making the peripheral smear due to its fragile nature.
  - **Platelets:** Initially the platelet count is normal. The bone marrow infiltration as well as autoimmune destruction of platelets associated with hypersplenism may result in decreased platelet count and a count below 100 x 109/L is associated with a worse prognosis.

**Hemoglobin:** Usually below 13 gm/dL and as the disease progresses, it may decrease below 10 gm/dL. This is due to marrow failure and associated autoimmune hemolysis may also be contributory, when present.

### Bone marrow

- **Cellularity:**hypercellular marrow.
- **Erythropoiesis:** Erythropoiesis is normal. Patients are prone to develop autoimmune diseases, most commonly directed against red cells or platelets. Such cases which result in hemotytic anemia show normoblasticerythroid hyperplasia.
- **Myelopoiesis:**Myelopoies is is normal in the initial stages of the disease.
- **Megakaryopoiesis:**Mega karyopoiesis is within normal limits.

As the neoplastic lymphocytes increase in number, they replace the normal cells of erythroid, myeloid and megakaryocytic series in the bone marrow. This results in anemia, neutropenia and thrombocytopenia and indicates that the disease is advancing.

### Special Tests

***Antiglobulin (Coombs) Test***

About 15 to 20% of patients manifest autoimmune hemolytic anemia and have positive direct Coombs test.

**Immunophenotype**

The tumor cells in CLL/SLL express the pan-B cell markers CD19 and CD20.

B cell CLL is characterized by aberrant expression of

T cell antigen CD5 (found only in a small subset of normal B cells). There is also weak expression of monoclonal surface immunoglobulin with k or l light chains.

**Cytogenetic Abnormalities**

Chromosomal translocations are rarely observed in both CLL and SLL. The common mutations associated are deletions of l3q14.3, 11q22-23, and 17p13.

About 20% of CLL show trisomy I2.

## Clinical Presentation of CLL:

### Clinical Presentation

- ***Age:*** Most of the patients at the time of diagnosis are between 50-60 years of age.
- ***Sex:*** More common in males than in females with a ratio of 2:1.

| Asymptomatic | Non specific symptoms | Symptoms from splenomegaly |
|---|---|---|
| About 25% of patients are often asymptomatic and are detected either because of nonspecific symptoms or routine blood examination for some other disease | • Fatigue<br>• Malaise<br>• Weight loss<br>• Anorexia | • ***Generalized lymphadenopathy:*** Initially the cervical lymph nodes are enlarged and in later stages there may be generalized lymphadenopathy. Involved nodes are rubbery, discrete, non-tender, small and mobile.<br>• ***Splenomegaly and hepatomegaly:*** This is observed in very few cases. Infiltration by CLL cells is seen in the splenic white and red pulp and in hepatic portal tracts resulting in enlargement of both organs.<br>• ***Immunological defects:*** CLL/SLL disrupts normal immune function, the mechanisms of which are not known. The pathogenic IgGs are produced by non-neoplastic, self-reactive B cells rather than tumor cells resulting in the following:<br>**Immune deficiency:** Hypogammaglobulinemia is common and is responsible for increased risk of opportunistic infections.<br>**Autoimmunity:** Patients may develop systemic autoimmune diseases, especially hemolytic anemia or thrombocytopenia due to autoantibodies. |

## Course and Prognosis of CLL:

*Course is variable and depends on Clinical stage of disease.*

| *Prognostic Factors of CLL* |
|---|
| • *Plasma β2 microglobulin level:* High levels are associated with a poor prognosis.<br>• *Presence of deletions of 11q and 17p*: Worse prognosis.<br>• *Bone marrow trephine biopsy*: Pattern of marrow infiltration.<br>• *Nodular and interstitial pattern of infiltration* has better prognosis than mixed and diffuse types.<br>• *Lack of somatic hypermutation:* Worse prognosis |

## Progression and Transformation of CLL:

CLL/SLL may transform to more aggressive tumors. These transformations are probably due to additional mutations resulting in rapid growth and are indicative of poor prognosis.

***B cell Prolymphocytic Transformation***

Transformation to B cell prolymphocytic leukemia is extremely rare. It is characterized by:

- Appearance of "prolyrnphocytes" in the peripheral blood (>10%).
  These prolymphocytes are large cells with a single prominent centrally placed nucleolus
- Worsening of cytopenias
- Increasing splenomegaly.

***Transformation to Diffuse Large B cell Lymphoma (Richter syndrome)*** (Found in 5 to 10% of patients)
Characterized by the development of a rapidly enlarging mass within a lymph node or the spleen.

# Chronic Myeloid Leukemia (CML)

## What is Chronic Myeloid Leukemia:

CML

Chronic myeloproliferative disorder from neoplastic transformation of a bone marrow stem cell that still retains capacity to differentiate along erythrocytic, megakaryocytic and granulocytic or monocytic lines.

### Pripheral blood picture

- StrikingLeucocytosis (Elevated WBC count)
  Both immature and mature farms in different Stages of maturation may be seen But
  ***Blood picture is dominated by Mature forms and precursor in the intermediate stages of differentiation***
  (Neutrophils, Metamyelocytes and Myelocytes)

  **Immature forms are less numerous**

  Blasts <5%
  Promyelocytes<10%

  (Cells are usually present in direct degree to the stage of maturation)

  **BasophillsEosinophils may be increased**
  - Elevated Basophils (often present)
  - Elevated Eosinophils (less common)
- **Thrombocytosis**
  Elevated platelet count if often present.Platelet count may be normal or sometimes elevated to strikingly high levels
- **Erythrocytes**
  Red blood cell morphology is normal.
  Patient is usually not anemic or only mildly anemic

### Bone marrow

- Bone marrow is hypercellular with left shifted myelopoesis
- Myeloid: Erythroid ratio is increased
- Myeloblasts comprises less than 5% of marrow cells

### Special Tests

- Cytogenetic Analysis for PhiladelphiaChromosome
  A small chromosome 22 caused by t (9; 22) translocation that results in bcr/abl fusion gene
- Reduced Leukocyte alkaline phosphatase levels(↓LAP)
  This indicates that although the total number of granulocytes is increased they are functionally impaired
- Serum levels of vitamin $B_{12}$proteins is ↑ed binding.

## Clinical Presentation in CML:

Clinical Presentation

**Common presenting features**

| Asymptomatic | Non specific symptoms | Symptoms from splenomegaly |
|---|---|---|
| Discovered incidentally during health screening tests | • Fatigue<br>• Malaise<br>• Weight loss | • Early satiety<br>• Left hypochondrial heaviness or left upper quadrant pain<br>*(CML is associated with massive splenomegaly)* |

Physical examination : Physical signs
- Splenomegaly (mild, moderate, massive), and sternal tenderness are characteristic
- Mild hepatomegaly may be present &lymphademopathy is unusual

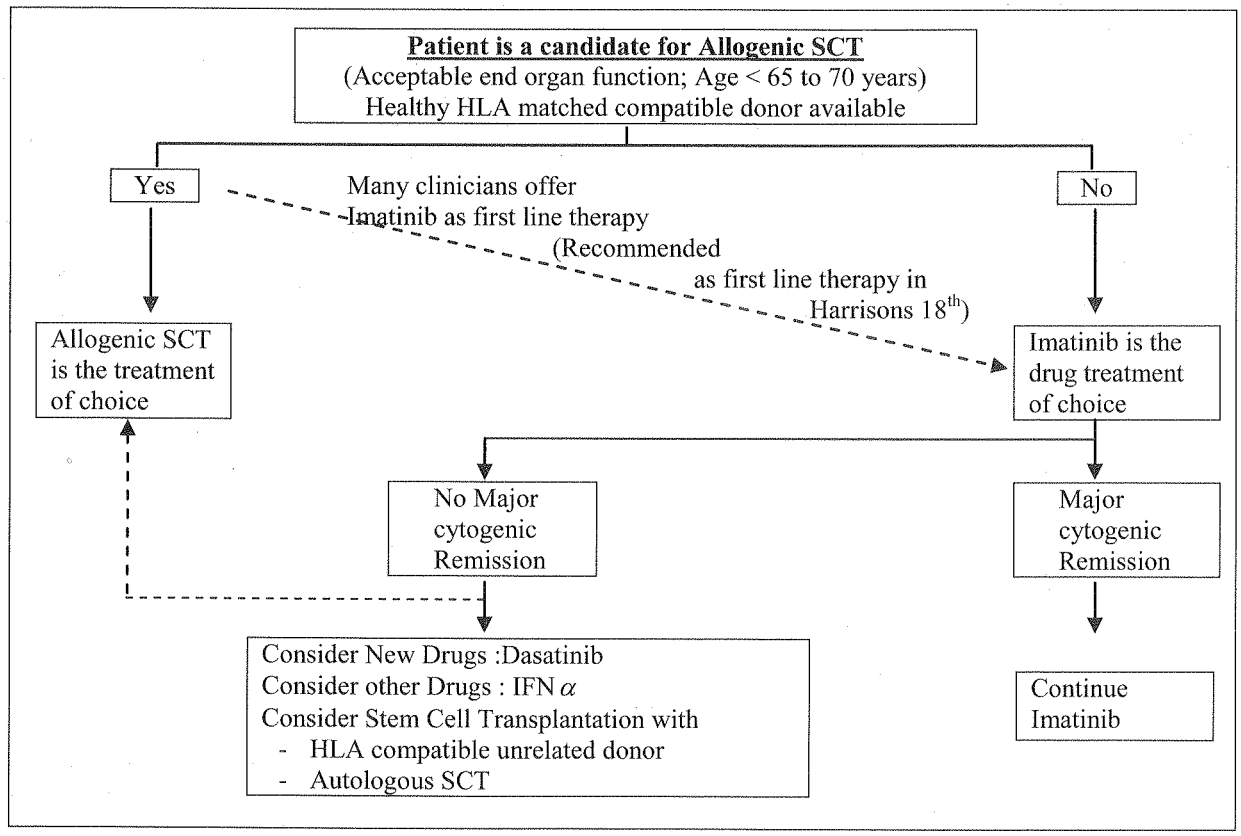
**Uncommon presenting features**

| Features related to Granulocyte /Platelet dysfunction |
|---|
| • *Infection*<br>• *Thrombosis*<br>• *Bleeding* |

| Leukostatic manifestations d/t severe Leukocytosis or thrombosis |
|---|
| • *Vasoocclusive disease*<br>• *Corebrovascular accidents*<br>• *Myocardial infarction*<br>• *Venous thrombosis*<br>• *Priaprism*<br>• *Visual disturbance*<br>• *Pulmonary insufficiency* |

## Treatment of CML

- The only curative treatment for CML is Allogenic Stem Cell Transplantation (SCT) (Allogenic bone marrow transplantation) [Q]
- The treatment of choice for CML is also Allogenic Stem Cell Transplantation (SCT) (Allogenic bone marrow transplantation) [Q]
- ***The drug treatment of choice for CML is Imatinib*** [Q]
- ***The initial treatment of choice for CML is drug treatment with Imatinib***
- *Interferon alpha (IFN α ) used to be the drug treatment of choice for CML when Imatinab was not available*




**Conditions presenting with raised HBF:**

**HbF is raised in following conditions**

- *Juvenile CML* [Q]
- βthalossemia [Q]
- Sickle cell anaemia [Q]
- Heriditary persistence of fetal haemoglobin (HPFF)

# Mycosis Fungoides

Mycosis fungoides is synonymous with Cutaneous T cell lymphoma.

**Clinical presentation and course:**

- Mycosis fungoides***has an indolent course.***
  *Most affected individuals have disease that remains localized to the skin for many years.*
  *It begins on the skin and may involve only the skin for years or decades*
- Presentation is with localized or generalized erythematous / eczematous skin lesions.
  Skin lesion progress from 'patch' stage to 'plaque stage' to cutaneous 'tumors' stage.
- Metastasis occurs in advanced stages :

| To lymph nodes | Peripheral circulation |
|---|---|
| | ***Sezary syndrome (Erythroderma and Circulating tumor cells)*** Seeding of the blood by melanoma cells is accompanied by diffuse erythema and scaling of the entire body surface (erythroderma). |

**Histology**

| Sezary - Lutzner cells | ***PautrierMicroabscesses*** |
|---|---|
| • Histological hall mark of Mycosis fungoides<br>• These are T helper ceil (CD4 positive) | Sezary - Lutzner cells characterstically form band like aggregates within the superficial dermis and invade the epidermis as single cells or small clusters called Pautrier'sMicroabscesses. |

**Treatment (Mycosis fungoides is not easily amenable to treatment)**

- ***The treatment of Mycosis fungoides is complex. Even early and aggressive treatment has not been proved to cure or prevent progression of the disease***. *-CMDT*
- *Cure has been possible with radiotherapy only in rare patients with early stage mycosis fungoides.*
- *Most of thetreatment for mycosis fungoides are 'palliative'.*

## Acute Lymphoid Leukemia (ALL)

**Classification of Acute Lymphoid Leukeia (ALL):**

| Immunologic Subtype | % of Cases | FAB Subtype | Cytogenetic Abnormalities |
|---|---|---|---|
| Pre-B ALL | 75 | L1, L2 | t(9;22), t(4, 11), t(1; 19) |
| T Cell ALL | 20 | L1, L2 | 14q 11 or 7q34 |
| BCell ALL | 5 | L3 | t(8; 14), t(8; 22), t(2;8) |

Immunophenotypic classification for ALL

| FAB classification | Immunologic classification | Phenotype | Incidence (% cases) | | Cytogenetic Abnormalities |
|---|---|---|---|---|---|
| Pre-B Cell | Early Pre-B | CD19, CD20-/+, CD10, CD34, TdT | 55 | 75 | t(9;22), t(4, 11), t(1; 19) |
| | Pre-B | CD19, CD20+/-, CD10, CD34-, cIgM, Tdt+/- | 20 | | |
| B cell | B cell | CD19, CD20, CD22, CD10+/-, CD34-, Tdt-, sIg | 5 | | 14q 11 or 7q34 |
| T cell | T cell | CD1, CD2, CD3, CD5, CD7, CD10+/-, CD34-/+, Tdt, dual CD4/CD8 | 20 | | t(8; 14), t(8; 22), t(2;8) |

**Prognostic factor for ALL:**

| **Determinants** | **Favourable** | **Unfavrourable** |
|---|---|---|
| White blood cell count | Low WBC count* | High WBC count* |
| ***Age*** | ***3-7 yrs*** | ***<1, > 10 yr*** |
| Gender | Female | Male |
| Ethnicity | White | Black |
| Node, Liver, spleen enlargement | Absent | Massive |
| ***Testicular enlargement*** | ***Absent*** | ***Present*** |
| Central nervous system leukemia | Absent | Overt (blasts + pleocytosis) |
| FAB morphological features | L1 | L2 |
| Ploidy | Hyperdiploidy | Hypodiploidy< 45 |
| DNA index | > 0.16 | < 0.16 |
| Cytogenenetic markers | Trisomies 4, 10 and/or 17<br>t(12;21) (telaml 1) | t(9; 22) [bcrabl]<br>t(4; 11) [mll af4]<br>t(1; 19) |
| Time to remission | < 14 d | > 28 d |
| Minimal residual disease | $< 10^{-4}$ | $> 10^{-3}$ |
| Immunophenotype | Early Pre-B cell | T cell |

**High WBC count is associated with a poor prognosis**

*Initial leukocyte count at diagnosis has proved to be an important prognostic factor in virtually every ALL study. Different studies (textbooks) quote different values for the initial WBC count that is associated with a poor prognosis but uniformly a high WBC count carries a poor prognosis.*

| Different text books | Favourable WBC count | Unfavourable WBC count |
|---|---|---|
| *Wintrobe's Hematology* | *< 10,000* | *> 20,000* |
| *Hoffman Hematology* | *< 50,000* | *> 50,000* |
| *Manual of Clinical oncology* | *<30,000* | *>30,000* |
| ***Inference*** | ***Low WBC count*** | ***High WBC count*** |

# Acute Myeloid Leukemia (AML)

## Prognostic Feature in Acute Myeloid Leukemia:

| Factor | Favourable | Unfavourable |
|---|---|---|
| **Clinical** | | |
| *Age* | *<45 yr* | *<2yr, >60yr* |
| *ECOG performance status* | *0-1* | *>1* |
| *Leukemia* | *De novo* | *Antecedent hematologic disorder, myelodysplasia, myeloproliferative disorder* |
| *Infection* | *Absent* | *Present* |
| *Prior chemotherapy* | *No* | *Yes* |
| *Leukocytosis* | *<25,000/mm3* | *>100,000/mm2* |
| *Serum LDH* | *Normal* | *Elevated* |
| *Extramedullary disease* | *Absent* | *Present* |
| *CNS disease* | *Absent* | *Present* |
| *Cytoreduction* | *Rapid* | *Delayed* |
| **Morphology** | | |
| *Auer rods* | *Present* | *Absent* |
| *Eosinophils* | *Present* | *Absent* |
| *Megaloblasticerythroids* | *Absent* | *Present* |
| *Dysplastic megakaryocytes* | *Absent* | *Present* |
| *FAB type* | *M2, M3, M4* | *M0, M6, M7* |
| **Surface/enzyme markers** | | |
| *Myeloid* | *CD34-, CD14-, CD13-* | *CD34+* |
| *HLA-DR* | *Negative* | *Positive* |
| *TdT* | *Absent* | *Present* |
| *Lymphoid* | *Cd2+* | *CD7+, CD56+ Biphenotypic (2 or more lymphoid markers)* |
| *MDR-1* | *Absent* | *Present* |
| **Cytogenetics** | | |
| *Cytogenetics* | *t(15;17), t(8;21), inv(16)* | *-7, del(7q), -5, del(5q), 3q21 and 3q26 abnormalities, complex karyotypes* |
| **Molecular markers** | | |
| *Fms-related tyrosine kinase-3 mutation* | *Absent* | *Present* |
| *Ecotropic viral integration site 1 expression* | *Absent* | *Present* |
| *Mixed-lineage leukemia partial tandem duplication* | *Absent* | *Present* |
| *Nucleophosphin mutation* | *Present* | *Absent* |
| *CCAAT/enhancer-binding protein-α mutation* | *Present* | *Absent* |
| *Brain and acute leukemia cytoplasmic gene expression* | *Absent* | *Present* |
| *Vascular endothelial growth factor expression* | *Absent* | *Present* |

## Auer Rods and Acute Myeloid Leukemia (AML)

Auer Rods are crystalline, refractile, azurophilic rod shaped structures made from alignment of granules that are typically seen in AML (may be seen in refractory anemia with excess blasts in transformation)

- *Auer Rods are most frequently seen in AML-M3 (95-100%) and AML-M2 (70%)*[Q]
- *Auer Rods are absent by definition in AML-M0*[Q]
- *Auer Rods are usually not seen in AML-M5a and AML-7*[Q]

**Auer Rods in AML**

| Most Frequently seen in (Typical Findings) | Absent in (By Definition) | May be seen in other subtypes(30-50%) |
|---|---|---|
| • AML M3 (95-100%)<br>• AML M2 (70%) | AML – M0<br>Usually not seen in AML 5a and AML 7 | *AML M1*<br>*AML M4*<br>*AML M6* |

## Plasma cell dyscrasias

Expansion of single clone of immunoglobulins secreting cells and a resultant increase in serum levels of a single homgenous immunoglobulin or its fragments.

**Myeloma**

- **Multiple Myeloma** — Multiple tumerous masses of plasma cells, scattered throughout the skeletal system
- **Solitary plasmacytoma** — Solitary Neoplastic mass of plasma cells found in the bone or soft tissue

**Waldenstrommacroglobulinemia**

- Diffuse infiltrate of Neoplastic B cells throughout bone marrow and lymph nodes, liver and spleen
- Neoplastic B cells produce only IgM. i.e. monoclonal component = IgM

**Heavy chain disease**

- Characterized by elevated levels in blood and urine of a specific heavy chain of immunoglobulins

**Monoclonal gammopathy of undetermined significance (MGUS).** This is the most common monoclonal gammopathy.

## Multiple Myeloma

### MULTIPLE MYELOMA

Malignant proliferation of plasma cells in the bone marrow results in production of large number of complete and incomplete immunoglobulins

Suppression of normal hematopoietic cells in marrow
- Anemia (normocytic normochromic)

Proliferation of plasma cells in bone and activation of osteoclasts activating factor
- *Lytic lesions* [Q] → Bone pain, Pathological fractures, Cord compression
- *Hypercalcemia*
  - Metastatic calcification (not dystrophic [Q])
  - Osteoporosis

**Increased number of abnormal immunoglobulins**

| | | | | |
|---|---|---|---|---|
| Precipitation in kidney (kidney damage) ↓ Bence Jones Light chain Proteinuria [Q] → ***Renal failure*** [Q] *(Amyloidosis may occur [Q])* | Ineffective defence against infections [Q] ↓ ***Recurrent Infections*** [Q] | Interference with clotting factors Amyloid damage of endothelium ↓ ***Bleeding tendency*** [Q] *(May be seen due to failure of antibody coated platelets to function properly or due to the interaction of M component with clotting factors I,II,V,VII or VIII)* | ***Hyperviscosity*** [Q] ↓ *Neurological* [Q] *Manifestations* - Vertigo, Tinnitus - *Headache* [Q] - *Visual disturbance* [Q] | ***Cryoglobulinemia*** *(Type-1)* • *Monoclonal Cryoglobulins are commonly seen in Multiple Myeloma* • *Raymond's phenomenon and impaired circulation may result if the M Component forms cryoglobulin* |

### The Classic Triad of Multiple Myeloma

**The classic triad of myeloma is:**

a) *Marrow plasmacytosis> 10%*
b) *Lytic bone lesions*
c) *Serum or urine 'M' component*

### Diagnosis and Staging of Multiple Myeloma (The Durie and Salmon myeloma diagnostic criteria)

- The Durie and Salmon myeloma diagnostic criteria are used widely in the United States and have been validated by large multicenter trials.
- The diagnostic criteria are divided into major and minor.
  *The diagnosis of Multiple Myeloma requires a minimum of one major and one minor criterion or three minor criteria as defined in the table below*
- Once the diagnostic criteria for multiple myeloma are met, Durie-Salmon clinical staging can be used to determine the stage of disease.

## Criteria for Diagnosis of Multiple Myeloma

**Major criteria**

1. *Plasmacytomas on tissue biopsy*
2. *Bone marrow plasmacytosis (> 30% plasma cells)*
3. *Monoclonal immunoglobulin spike (M spike) on serum electrophoresis:*
   *IgG > 3.5 g/dl or*
   *IgA > 2.0 g/dl*
   *κorλ light-chain excretion > 1.0 g/d on 24-h urine protein electrophoresis.*

**Minor criteria**

a. *Bone marrow plasmacytosis (10-30% plasma cells)*
b. *Monoclonal immunoglobulin spike present but of lesser magnitude than in 3*
c. *Lytic bone lesions*
d. *Supressed Uninvolved Immunoglobulin*
   *Normal IgM <50mg/dl or*
   *Normal IgA <100 mg/dl or*
   *Normal IgG <600 mg/dl.*

*Any of the following sets of criteria will confirm the diagnosis.*

*Any two major criteria*
*Major criterion 1 plus minor criterion b, c or d*
*Major criterion 3 plus minor criterion a or c*
*Minor criteria a, b and c or a, b and d*

## Comparisonof MGUS, Indolent myeloma and Smoldering myeloma:

| | MGUS | SMM | IMM | Multiple Myeloma |
|---|---|---|---|---|
| **Plasma cell (BM)** | <10% | 10-30% | >30% | >30% |
| **M-component** | IgG<3.5,<br>IgA<2 | IgG>3.5,<br>IgA>2 | IgG 3.5-7,<br>IgA 2-5 | IgG >3.5/dl;<br>IgA >2g/dl |
| **Lytic bone lesion** | None | None | ≤3 | Present |
| **Symptoms/Infection**<br>- *Anemia*<br>- *Renal insufficiency*<br>- *Hypercalcemia* | None | None | None | Present |

# Disorders of Bleeding and Coagulation

## Coagulation Cascade

**Factors involved in exclusively Intrinsic Pathway**

- *Factor XII*
- *Factor XI*
- *Factor IX*
- *Factor VIII*

Prekallekrein
HMW kininogen

**Factors involved in exclusively in Extrinsic Pathway**

- ***Factor VII***
- TissueThromboplastin (Formerly called Factor III)

**Factors Involved in Common Pathway**

*Factor X*
*Factor V*
*Factor II*
*Factor I*
*Factor XIII*

**APTT**
Measure the time required to generate Thrombin and Fibrin polymers via the intrinsic and common pathway

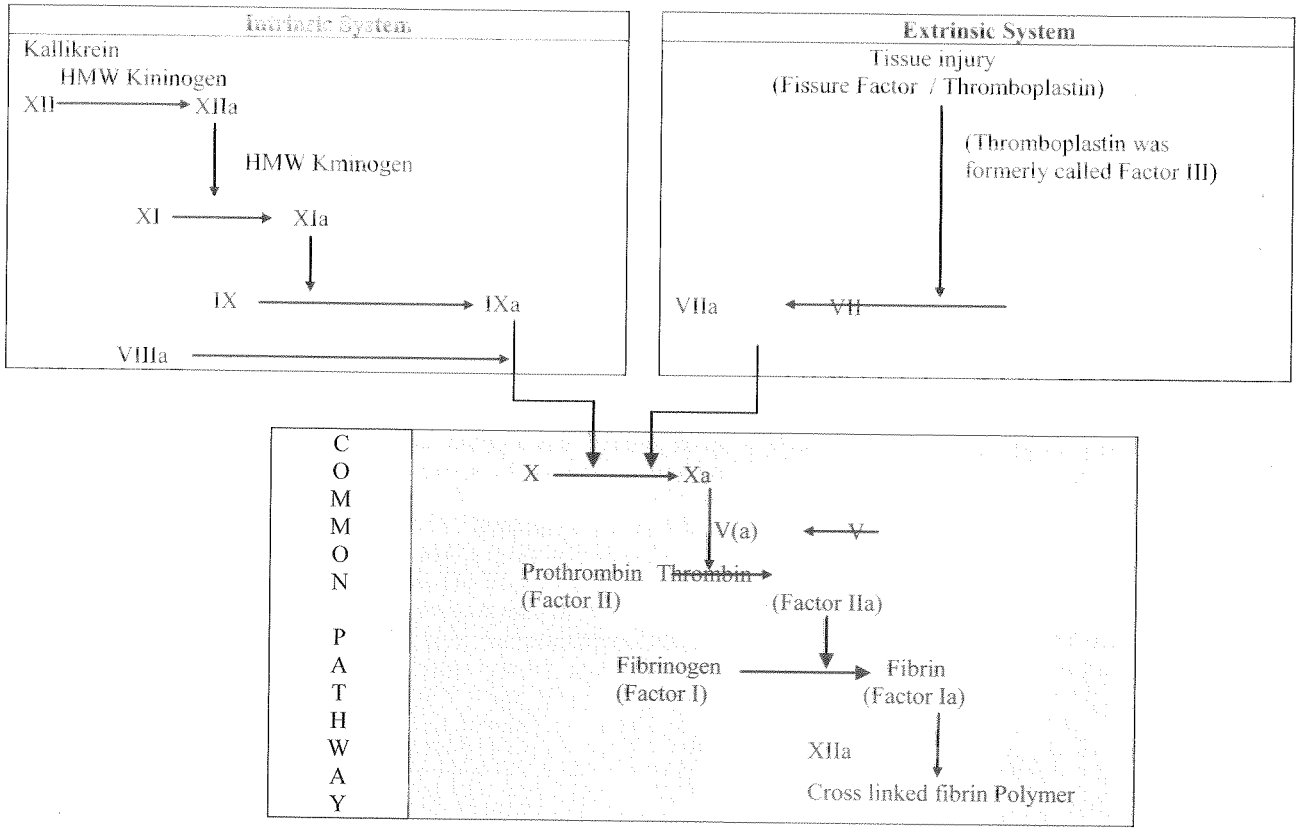
Intrinsic pathway + Common Pathway

**APTT assays thus reflect the activity of**
*XII, XI, IX, VIII + X, V, II, I*

**PTT**
Measures the true required to generate thrombin and fibrin polymers via the extrinsic and common pathway

Extrinsic pathway + Common Pathway

**PTT assays thus reflect the activity of**
*VII + X, V, II, I*



## Approach to a patient with isolated prolongation of activated Partial Thromboplastin time (aPTT)

- The Partial Thromboplastin Time (aPTT) is a performance indicator measuring the efficacy of both the '*intrinsic system*' *and the 'common' coagulation pathway.*
- ***Isolated prolongation of aPTT (normal PT)*** may indicate:
  - *Coagulation Factor Deficiency (Factor VIII, IX, XI, XII, Prekallikrein, HMWK)*
  - *Presence of Antiphospholipid Antibodies especially Lupus Anticoagulant*
  - *Use of heparin (or contamination of sample with Heparin)*
  - *Specific coagulation factor Inhibitors (factor VIII inhibitor or Factor IX or XI (rare) inhibitor)*
- The ***presence or absence of bleeding manifestation*** even after major surgery may narrow down the differential diagnosis.

| Isolated Prolongation of aPTT with no bleeding manifestation | Isolated prolongation of aPTT with bleeding manifestation |
|---|---|
| • Specific Coagulation Factor Deficiencies<br>- *Factor XII Deficiency*<br>- *Prekallekrien*<br>- *HMW Kininogen Defect*<br>• ***Presence of Lupus Anticoagulant*** | • Specific Coagulation Factor Deficiencies<br>- *Factor VIII defect*<br>- *Factor IX defect*<br>- *Factor XI defect*<br>• Specific Coagulation Factor Inhibitors<br>- *Factor VIII inhibitor*<br>- *Factor IX inhibitor or Factor XI inhibitor* |

Isolated Prolongation of aPTT (Normal PT)

↓

Mixing Study
*Patient's plasma is mixed with normal plasma*

↓

Does the mixing study correct the aPTT?

Yes → Mixing Study: *Patient's plasma is mixed with normal plasma. (Initially in a dilution of 50:50)* *If abnormality corrects, a factor deficiency (Factor VIII, IX or XI) is likely.* *If abnormality does not disappear the sample is believed to contain an 'Inhibitor'*

Yes → **If patient is bleeding,** *Consider deficiency of FVIII, IX, or XI, or VWD.* Take further history and send appropriate assays.
**If patient is not bleeding,** *Consider deficiency of FXII, HMWK, or PK*

No ↓

***Is the patient bleeding?***

Yes → ***Patient may have an inhibitor to factor VIII.*** *Send incubated mixing study. Send FVIII activity, Bethesda titer.*
*If studies not consistent with FVIII inhibitor, then* ***consider acquired VWD or inhibitor to FIX or FXI*** *(very rare).*

***Patient may have heparin contamination of sample.*** *Ensure that heparin is not responsible for lab abnormality(Either repeat test, making sure not to draw from a heparinized line. May also run TCT/RT, anti-Xa level, or treatsample with heparinase or adsorb heparin using heparin-binding using, or do TCT ± protamine to determine whether heparin is responsible for abnormality.)*

↓ No

***Patient may have a Lupus Anticoagulant.*** *Send lupus anticoagulant evaluation.*
*If LA evaluation is negative,* ***consider inhibitor to FXII***

## Causes of isolated Prolongation of PT

| Cause of Isolated prolongation of PT (CMDT) |
|---|
| ***Vitamin K deficiency*** |
| *Warfarin therapy* |
| *Liver disease* |
| *Factor VII deficiency* |

## Causes of Prolonged PT and APTT

| Causes of Prolonged PT and APTT |
|---|
| • Coagulation Factor Deficiency (Factor II, V, X or fibrinogen) |
| • Use of oral anticoagulants (Warfarin) |
| • Disseminated Intravascular coagulation |
| • Severe vitamin K deficiency |
| • Liver Disease (Severe Hepatic Insufficiency) |
| • Heparin in sample (at high concentrations only) |
| (Heparin is typically associated with prolonged APTT & normal PT) |



## Bleeding and Coagulation Disorders

| Spontaneous Hemarthrosis<br>Spontaneous Muscle Bleed | Spontaneous Mucosal Bleeding |
|---|---|
| • ***Spontaneous Hemarthosis and spontaneous muscle Hematomas are a hallmark of moderate or severe factor VIII and IX deficiency (Hemophilia)***<br>• *These can also be seen in moderate or severe deficiencies of other coagulation factors like fibrinogen, prothrombin and factor V, VII, & X*<br>• *These are rarely seen in other bleeding disorders.* | • Mucosal bleeding symptoms are more suggestive of underlying platelet disorders or Von Willebrand disease<br>(Disorders of primary hemostosis or platelet plug disorders) |

## Von Willebrand disease and Hemophillia

### Von Willebrand

Von Willebrand disease is caused by a defect of deficiency of VWF factor and presents as bleeding and coagulation disorder.

VWF factor is required for normal platelet adhesion and aggregation.
VWF factor is the plasma carrier for factor VIII which is required for intrinsic pathway of the coagulation cascade.

Von Willebrand Factor (VWF)

VWF is essentially composed of the following components

**Factor VIII – VWF antigen**

- This antigen binds factor VIII and acts as a carrier for factor VIII in the plasma.
- It protects factor VIII from rapid proteolytic destruction in plasma

↓ Defect in VWF (VW disease) will result in

- Decreased levels of factor VIII$^{Q}$
- Decreased activity of factor VIIIc$^{Q}$

↓

- Defect in intrinsic pathway of coagulation cascade

- Prolonged PTT$^{Q}$
- PT is normal as there is no defect in extremely pathway$^{Q}$

This antigen also acts as a mediator for initial adhesion of platelets to the vessel wall.

↓ Defect in VWF will result in

Defect in platelet function (Decreased Adhesion)

↓

Prolonged bleeding time$^{Q}$

**Risocetin cofactor (VWF activity)**

This cofactor is required for ristocetin induced platelet aggregation

Ristocetin is an antibioctic that induces platelet aggregation

↓ Defect in VWF activity will result in

Impaired platelet aggregation in response to Ristocetin$^{Q}$

## Features of VWF and differences with Haemophilia A

| Feature | Hemophilia A | Von Willebrand Disease |
|---|---|---|
| Inheritance | ***Sex linked***<br>Clinical disease limited to Men /boys<br>***(Extremely rare in females)*** | ***Autosomal (Most commonly A-dominant)***<br>Clinical disease may be seen in both boys & girls |
| Factor VIIIc | Decreased | Decreased |
| VWF | Normal | Decreased |
| Ristocetin cofactor | Normal | Decreased |
| Common Presentation | Features of clotting disorder<br>Skin/Mucosal bleeding –<br>***Hemarthrosis ++*** | Features of bleeding disorder ± clotting disorder<br>Skin/Mucosal bleeding +<br>***Hemarthrosis+*** |
| Bleeding Time | Normal | Prolonged |
| ***APTT*** | ***Prolonged*** | ***Prolonged (may be normal)*** |
| ***PT*** | ***Normal*** | ***Normal*** |
| Thrombin Time | Normal | Normal |
| Fibrinogen | Normal | Normal |
| Platelet aggregation in Response to Ristocetin | Normal | Decreased |

## Differences betweenHaemophilia A and Hemophilia B

| | Haemophilia A (Classical hemophilia) | Haemophilia B (Christmas disease) |
|---|---|---|
| **Defect** | Deficiency of coagulant subunit of factor i.e (VIII c)<br>Factor VIII = VIII c + VWF | Deficiency/absence of factor IX. |
| **Pathway of coagulation affected** | Intrinsic Pathway | Intrinsic pathway |
| **Whole blood clotting time** | ↑ | ↑ |
| **PTT** | ↑ | ↑ |
| **PT** | N | N |
| **BT** | N | N |
| **Platelet count** | N | N |
| **Tourniquet test** | N | N |

## Disorders of Platelet Number and Function

### Thrombocytopenia

**Causes Of Thrombocytopenia**

**Decreased Production (Decreased Megakaryocytes in marrow)**

1. *Aplastic anemia PNH* [Q]
2. Marrow infiltration:
   - *Leukemia* [Q]
   - *Metastasis* [Q]
   - *Radiation* [Q]
3. *Vitamin $B_{12}$ & Folic acid deficiency* [Q] *(associated megaloblastic anemia)* [Q]
4. Hereditary:
   *Autosomal dominant form of Wiskott Aldrich syndrome* [Q]

**Increased Destruction (Normal or Increased Megakaryocytes in Marrow)**

*Immune mechanism*

1. *ITP* [Q]
2. *SLE* [Q]
3. *Post transfusion* [Q]
4. Neonatal: due to maternal IgG antibodies
5. *Drugs* [Q]:
   - Quinine
   - Gold
   - Sulfonamides

*Non-Immune (↑consumption)*

1. TTP (↑consumption)
2. HUS
3. *DIC* [Q]
4. Valve prosthesis
5. Hypersplenism

### Disorders of Platelet Function

Classification of congenital disorder of platelet function:

1. Defects in platelet-vessel wall interaction (disorders of adhesion)
   - ***(a) VonWillebrand disease (deficiency or defect in plasma vWF)***
   - ***(b) Bernard-Soulier syndrome (deficiency or defect in GPIb)***
2. Defects in platelet-platelet interaction (disorders of aggregation)
   - *(a) Congenital afibrinogenemia (deficiency of plasma fibrinogen)*
   - ***(b) Glanzmannthrombosthenia (deficiency or defect in GPIIb-IIIa)***
3. Disorders of platelet secretion and signal transduction
   - *(a) Storage pool deficiency*
   - *(b) Quebec platelet disorder*
   - *(c) Chediak Higashi syndrome*
   - *(d) Gray Platelet syndrome*
   - ***(e) Wiskott-Aldrich syndrome***
4. Disorders of platelet coagulation – protein interaction
   *(a) Defect in facorVa-Xa interaction on platelets (Scott syndrome)*

## Wiskot Aldrich syndrome:

***Wiskott Aldrich Syndrome (WAS)***
***(X linked Recessive inheritance)***

**Characteristic Triad**

**Eczema**
*Eczematoid Rash*

**Thrombocytopenia**
*Repeated Bleeding episodes*

Platelet in WAS
- ↓ed Platelet count (Thrombocytopenia)
- ↓ed Platelet size (characteristic) (Number and morphology of Megakaryocytes in marrow is normal)
- *Impaired platelet aggregation response*

**Immunodeficiency**
***Repeated Infections***

Immunodeficiency in WAS
- ↓IgM
- ↑IgE
- IgA and IgG are usually normal
- ↓antibody response to uncongugatedpolysachharide antigens and protein antigens
- ↓ T cell (Acquired T deficiency) (eventually acquire severe T cell deficiency)

**Bernard SoulierSyndrome andGlanzmann'sthrombasthenia**

*(Intrinsic platelet defects to adhesion and aggregation.)*
Platelet adhesion and aggregation are modulated by glycoprotein receptors located on platelet surface.

**GpIb / Ix**
- Mediates ***platelet adhesion***
- *VWF facilitates* platelet adhesion by binding to this receptor

**GpIIb / IIIa complex**
- Mediates ***platelet aggregation***
- *Fibrinogen facilitates* platelet aggregation via sites on this receptor

Loss or defect in above glycoprotein receptors leads to rare platelet disorders causing bleeding

**Bernard Soulier Syndrome**
- Autosomal recessive disorder
- Deficiency / dysfunction of GpIb / Ix Receptor
- ***Platelets cannot adhere*** to subendothelium because of lack of above receptors for VWF which mediates platelet adhesion
- ***Platelet aggregation to largely normal platelet aggregation is normal in response to standard agonists (collagen ADP, thrombin / but platelet fail to aggregate in response to ristocetin as it acts by a different mechanism***

Other laboratory parameters
- ***Thrombocytopenia may be present***
- ***Platelets on smears are abnormally large***
- Bleeding time is abnormally prolonged
- VWF factor levels in plasma are normal

Clinical presentation
- Recurrent episodes of severe mucosal haemorrhage

**Glanzmann'sthrombasthenia**
- Autosomal recessive disorder
- Deficiency / dysfunction of GpIIb / III a complex
- ***Platelets cannot aggregate*** because of lack of above receptors for fibrinogen which form the bridges between platelets during aggregation.
- ***Platelet aggregation is largely abnormal. Platelet fail to aggregate in response to standard agonists, (ADP, collagen, thrombin) as these require fibrinogen binding, but aggregate normally to ristocetin as it cause platelet clumping by a different mechanism.***

Other laboratory parameters
- Platelet number is usually normal
- Platelet morphology is usually normal
- Bleeding time is abnormally prolonged
- VWF factor level in plasma are normal

Clinical presentation
- Recurrent episodes of severe mucosal hemorrhage

**Note :VonWillebrand's disease** : ***Platelet aggregation studies with standard agonists ADP, collagen, thrombin are normal but platelet aggregation in response to ristocetin may be subnormal (CMDT 2006 / 524).***

## Idiopathic Thrombocytopenic Purpura

***Idiopathic thrombocytopenic purpura*** *is a disease characterized by severe reduction of platelet numbers, caused by immune destruction of platelets. The mechanism of ITP appears to be immune complexes containing antibodies, which react with platelets and lead to their immunological destruction.*

Immune Thrombocytic Purpura (ITP)
*(Idiopathic Thrombocytopenic Purpura)*

Autoimmune Antibodies against Platelets

From response to ***previous viral infection***[Q] (Acute ITP) or From underlying immune dysregulation (chronic ITP)

↓

*Platelet destruction*

Thrombocytopenia

**Clinical manifestations**

Clinical signs and symptoms of ITP are reflective of thrombocytopenia (Bleeding manifestations due to decreased platelet count)

| **Characteristic Clinical Features** | ***Clinical features that are characteristically unusual and suggest the possibility of other diagnosis*** |
|---|---|
| Bleeding and haemorrhages from small venules or capillaries<br>• *Spontancouspetechiae*<br>• *Spontaneous echymoses*<br>• *Spontancous mucosal bleeding*<br>• *Easy Bruisibility*<br>• *Spleen is normal in size* | • *Frequent Bleeding and haemorrhages from larger veins and arteries and bleeding into joints (Suggest coagulation disorders)*<br>• *Splenomegaly and Lymphadenopathy are unusual/rare and their presence should lead one to consider other diagnosis.* |

**Laboratory Features**

- Isolated thrombocytopenia
- Platelet Antibodies
- Normal or increased number of megakaryocytes on bone marrow examination

Features of bleeding disorder
- Bleeding time is prolonged
- Tests of coagulation are essentially normal
  - Normal PT
  - Normal APTT
  - Normal Fibrinogen
  - Normal Fibrinogen Degradation products
  - Normal levels of coagulation factors

*'Hepatomegaly, splenomegaly and lymphadenopathy are notably absent in ITP, and their presence should initiate an investigation for other possible underlying illnesses associated with thrombocytopenia'- Oski's 2nd/463*

### Features of Acute and Chronic Idiopathic Thrombocytopenic Purpura (ITP):

ITP occurs in two forms, namely acute ITP and chronic ITP. Acute ITP and chronic ITP differ in incidence, prognosis and therapy

| Features | Acute ITP | Chronic ITP |
|---|---|---|
| Peak age of incidence | Children, 2-6 yr | Adults 20-40 yr |
| Sex predilection | None | 3:1 female to male |
| Antecedent infection | Common 1-3 wk before | Unusual |
| Onset of bleeding | Abrupt | Insidious |
| Hemorrhagic bullae in mouth | Present in severe cases | Usually absent |
| Platelet count | <20,000 /μl | 30,000-80,000/μl |
| Eosinophilia and lympocytosis | Common | Rare |
| Duration | 2-6 wk; rarely longer | Months or years |
| Spontaneous remission | Occur in 80% of cases | Uncommon |

### Treatment Modalities for ITP:

**Common Treatment Modalities for ITP** *(Platelet count <20,000/μl or significant mucosal bleeding)*

- *Corticosteroids*
- *IV Immunoglobulins / gamma globulins*
- *Additional Immunosupressive agents (Rituximab / Anti CD 20 Antibody)*
- *Splenectomy*

## Thrombotic Thrombocytopenic Purpura

**Thrombotic Thrombocytopenic purpura** is a disorder of 'vessel wall'$^{Q}$characterised by lesions in arteriolar walls $^{Q}$ in various organs that initiate formation of **localised platelet thrombi and fibrin deposits at various sites.**

**Clinical Pentad of TTP**

| | | | | |
|---|---|---|---|---|
| **Microangiopathic Hemolytic Anemia**$^{Q}$(Coomb's negative)<br>- Haemolysis$^{Q}$<br>- Fragmentation $^{Q}$ of RBC's<br>- Increased LDH (elevated due to intra- vascular hemolysis)$^{Q}$ | **Thrombocytopenia** $^{Q}$ (due to consumption of platelets) | **Decreased Renal Function**$^{Q}$(due deposits in the Renal Vasculature.) | **Disturbed Neurological function** $^{Q}$<br>Characteristically diffuse and non focal eg.<br>- Confusion<br>- Aphasia<br>- Alteration in consciousness | **Fever** |

| **Tests of coagulation are essentially normal** $^{Q}$ |
|---|
| - Normal PT $^{Q}$ |
| - Normal APTT $^{Q}$ |
| - Normal Fibrinogen concentration $^{Q}$ |
| - Normal Fibrin degradation Products $^{Q}$ |

***Thus: PENTAD as mentioned above + normal coagulation tests: PATHOGNOMIC OF TTP***

## DIC or Disseminated Intravascular Coagulation

DIC or Disseminated Intravascular Coagulation, is a complex thrombohaemorrhagic disorder characterized by the following sequence of events in general:

| **Events** |
|---|
| 1. Intravascular activation of coagulation by *both intrinsic and extrinsic mechanism.* $^{Q}$ |
| 2. A thrombotic phase |
| 3. Consumption phase, wherein most coagulation factors and platelets are consumed. |
| 4. Stage of secondary fibrinolysis, at site of intravascular coagulation. |
| **Laboratory findings** are in accordance with the above pathogenic mechanisms : |
| 1. *Platelets count, coagulation factors and fibrinogen level: are decreased* $^{Q}$ or 'consumed'. As a result of above: The *bleeding time as well as the coagulation time both are prolonged* $^{Q}$therefore<br>- *PTT: increased* $^{Q}$<br>- *PT: increased* $^{Q}$<br>- *Thrombin time : increased* $^{Q}$ |
| 2. Increased secondary fibrinolysis accounts for<br>- *raised plasmin levels* $^{Q}$<br>- *raised levels of fibrin degradation product (FDP).* $^{Q}$ |
| 3. The thrombolic phase accounts for *features of microangiopathichaemolytic anemia.* $^{Q}$<br>- *presence of schistiocytes, spherocytes, burr cells, halmet cells in the peripheral film.* $^{Q}$ |
| **Some question asked:**<br>• Most important treatment is : finding a reversible cause and *treatment of the cause* $^{Q}$<br>• *Finding in DIC, that correlates best and most closely with bleeding is : fibrinogen level* $^{Q}$<br>• Most common site for thrombin formation in DIC is : Brain $^{Q}$(Brain > heart > lung > kidney > adrenal > liver)<br>• DIC is related to 2 very important endocrine manifestations :<br>a. *Adrenals - FredrichHausen Syndrome.* $^{Q}$<br>b. *Pituitary - Sheehan's Syndrome.* $^{Q}$ |

# Antiphospholipid syndrome (APS)

## Antiphospholipid syndrome (APS)

- Defined by a clinical association of antiphospholipid antibodies and Hypercoagulability
- Considered a systemic autoimmune disease which is charachterized by recurrent thrombosis or pregnancy complications, along with the presence of Antiphospholipid antibodies.

Primary APS : No cause is identified | Secondary APS : Defined cause like SLE is identified

### Important Clinical Features

**Vascular Thrombosis**

- *Recurrent arterial or venous thrombosis* in any tissue or organ is the *most common presentation*

**Pregnancy morbidity**

- *Recurrent spontaneous Abortions*[Q]
- *Pregnancy induced Hypertension*[Q] *(Preeclampsia and ecelampsia)*
- *Placental Insufficiency/Abruption*[Q]
- *Intrauterine Growth Retardation*[Q]

### Important Laboratory Features

- *Elevated Anticardiolipin antibodies* [Q] *(IgG or IgM)* [Q]
- *Elevated Anti β -2 glycoprotein-1 Antibody* [Q]
- *Presence of Lupus Anticogulant (LA) in plasma* [Q]
- *Thrombocytopenia* [Q]
- *Haemolytic anemia* [Q] *(Coomb's positive)*

***Venous thrombosis***
(More common)

- *DVT is the most*[Q] *common manifestation*
- *Pulmonary Embolism*[Q]
- Pulmonary hypertension from thromboembolic disease

Arterial thrombosis
(less common)

| CNS | Heart | Lungs | Kidney | Bones | Others |
|---|---|---|---|---|---|
| *Stroke*[Q] (Cerebral vessel occlusion) | *Myocardial infarction*[Q] (coronary occlusion) | *Pulmonary Hypertension*[Q] (Pulmonary artery occlusion) | Glomerular Thrombosis *Renal Artery thrombosis*[Q] | *Avascular*[Q] *Necrosis* | |

Evan's Syndrome refers to the clinical association of Autoimmune Thrombocytopenia and Autoimmune Hemolytic anemia. Evan's Syndrome has been reported in 10 percent of patients with Antiphospholipid syndrome

## Diagnostic Criteria for Antiphospholipid Syndrome

***Definitive Antiphospholipid Syndrome is said to be present <u>if atleast one of the clinical criteria and one of the laboratory criteria are met</u>***

### Clinical Criteria

- **<u>Vascular Thrombosis (Arterial and/or Venous)</u>**
  One or more clinical episodes of arterial, venous or small vessel thrombosis in any tissue or organ.
- **<u>Pregnancy morbidity</u>**
  a. <u>*One or more unexplained deaths*</u> of a morphologically normal fetus at or<u>*beyond the 10th week of gestation*</u>, with normal fetal morpholoogy
  b. <u>*One or more premature births*</u> of a morphologically normal neonate <u>*before the 34th week of gestation*</u> because of:
  (a) eclampsia or severe preeclampsia
  (b) placental insufficiency
  c. <u>*Three or more unexplained consecutive spontaneous abortions before the 10th week of gestation*</u>, with maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes excluded.

### Laboratory Criteria

- **<u>Anticardiolipin Antibody</u>** of IgG and /or IgM isotype in serum or plasma *on 2 or more occasions, at least 12 weeks apart*
- **<u>Lupus anticoagulant</u>** present in plasma, *on 2 or more occasions at least 12 weeks apart*
- **<u>Anti-$\beta_2$- glycoprotein-1 antibody</u>** of IgG and or IgM isotype in serum or plasma, present *on 2 or more occasions, at least 12 weeks apart*

*'The mainstay of treatment of Antiphospholipid Syndrome is Warfarin' – Harrison*

## Bleeding manifestations due to vitamin deficiency

### Vitamin K dependent Coagulation Factors / Proteins :

### Vitamin K dependent Coagulation Factors / Proteins

- Six proteins involved in clotting require conversion of a number of glutamic acid residues to γ - carboxyglutamic acid residues before being released into circulation
- This process of γ (gamma) carboxylation occurs in the liver and requires vitamin k and hence these proteins are called vitamin – K dependent
- These include coagulation factors II, VII, IX and X as well as protein C and protein S.

| Vitamin K dependent proteins involved in clotting |
|---|
| • ***Coagulation Factor II*** $^{Q}$ ***(Prothrombin)*** |
| • ***Coagulation Factor VII*** $^{Q}$ ***(Proconvertin)*** |
| • ***Coagulation Factor IX*** $^{Q}$ ***(Christmas factor)*** |
| • ***Coagulation factor X (Stuart Prover Factor)*** |
| • *Protein C* $^{Q}$ |
| • *Protein S* $^{Q}$ |

### Bleeding manifestations due to vitamin deficiency

| VITAMIN C | VITAMIN K |
|---|---|
| • Vitamin C is required for synthesis of collagen which forms part of capillary walls. | • Vitamin K dependent factors include Factor II, VII, IX, X |
| • Vitamin C deficiency leads to increased capillary wall fragility and hence increased manifestations of haemorrhagic areas such as– | • In vitamin K deficiency bleeding occurs due to lack of coagulation factors |
| - *over lower extremities* $^{Q}$ | |
| - *around hair follicles* $^{Q}$ | |
| - *nailbeds* $^{Q}$ | |
| • Patient presents with | • Patient presents with |
| - increased bleeding time $^{Q}$ | - increased clotting time $^{Q}$ |
| - normal PTT, PT, TT $^{Q}$ | - increased PTT, PT, TT $^{Q}$ |
| - normal clotting time $^{Q}$ | - normal bleeding time $^{Q}$ |

## Conditions predisposing to Thrombosis

| Abnormality | Arterial | Venous |
|---|---|---|
| Factor V Leiden mutation | — | + |
| Prothrombin | — | + |
| ***Antithrombin III*** | — | + |
| ***Protein C*** | — | + |
| ***Protein S*** | — | + |
| ***Homocysteinemia*** | + | + |
| Antiphospholipid syndrome | + | + |

| | | |
|---|---|---|
| *Most common genetic cause for thrombophilia* | : | *Factor V Leiden* |
| *Most common congenital cause of venous thrombosis* | : | *Factor V Leiden* |
| *Most common hereditary blood coagulation disorder* | : | *Factor V leiden* |

# Methaemoglobinemia

## Methaemoglobinemia

- Methaemoglobinemia is an uncommon but distinct cause of central cyanosis in the absence of hypoxemia or cardio vascular compromise
- Methaemoglobinemia occurs when a significant concentration of hemoglobin (Hb) is oxidized to methaemoglobin (Met Hb)

> *When the haemmoety (iron atoms) of Hb molecule encounter a strong oxidizing agent iron loses an electron and switches from the Ferrous ($2^+$) to Ferric ($3^+$) state turning Hb to 'Met Hb'*

- Methaemoglobin has such high oxygen affinity that virtually no oxygen is delivered

## Presentation

- Methaemoglobinemia most commonly presents as *cyanosis unresponsive to supplemental oxygen*

> The most notable physical examination finding is generalized cyanosis which can manifest as muddy brown dark mucus membranes before proceding to global skin discolaration

- 'The charachteristic***muddy appearance(chocolate brown)*** of freshly drawn blood can be a critical clue'

*- Harrison's 18th/858*

*Blood appears dark brown, brownish, muddy or chocolate in colour immediately after withdrawal. In contrast to normal venous blood, the color does not change with addition of oxygen or agitation in the air'- *Diffirential diagnosis in Internal Medicine (Thieme) 2007/709*

> Methaemoglobinemia>15% cause symptoms of cerebral ischaemiaMethaemoglobinemia> 60% is usually lethal

## Diagnosis

- *The best diagnostic test for Methaemoglobinuria is 'Methaemoglobin Assay'*

## Treatment

- The most effective emergency management for methaemaglobinemia is *administration of Methylene blue*$^{Q}$ which serves as an antidote (introvenous)

> *Methylene blue is not effective in patients with methaemoglobinemia due to Hemoglobinopathy M*$^{Q}$ *(Haemoglobin M)*
> Methylene blue is *contraindicated in patients with G6 PD deficiency*$^{Q}$ since it can cause severe hemolysis due to its potential for oxidation

# QUESTIONS

## Hypochromic Microcytic Anemias

### Differential Diagnosis/Approach

1. Which of the following conditions is associated with microcytic hypochromic anemia: *(AIIMS Dec 94)*
   A. Sickle cell Anemia
   B. Thallassemia
   C. Fanconi's anemia
   D. Hereditary spherocytosis
2. All of the following cause microcytic hypochromic anaemia, *except*: *(AIIMS Dec 97)*
   A. Lead poisoning
   B. Thalassemia
   C. Iron deficiency
   D. Fanconi's anemia
3. All of the following cause Microcytic Hypochromic anemia *except:* *(AI 1995/AIIMS 1997)*
   A. Lead poisoning
   B. Thalassemia
   C. Iron deficiency anemia
   D. Fanconi's anemia
4. Which of the following are not associated with microcytic hypochromic RRCs on Peripheral smear?
   A. Iron Deficiency Anemia *(PGI 2009)*
   B. Lead
   C. Sideroblastic anemia
   D. Sickle Cell Anemia
   E. Hereditary spherocytosis
5. Which of the following is not expected in a case of Microcytic Hypochromic Anemia: *(NBE)*
   A. Reduced serum Iron
   B. Reduced Total RBC distribution Width
   C. Normal Ferritin levels
   D. Increased TIBC
6. Which of the following is not expected in a case of Microcytic Hypochromic Anemia *(NBE)*
   A. Reduced serum iron
   B. Increased serum ferritin level
   C. Decreased TIBC
   D. Decreased Free Erythrocyte protoporphyrin
7. A patient presents with Microcytic Hypochromic anemia. Serum iron levels and TIBC are decreased. Likely diagnosis is: *(NBE)*
   A. Iron deficiency anemia
   B. Anemia of chronic disease
   C. Thalassemia
   D. Sideroblastic anemia
8. Anemia of Chronic disease can be differentiated from Iron deficiency anemia by: *(PGI 2009)*
   A. ↑ TIBC
   B. ↓ TIBC
   C. ↑ S.ferritn
   D. ↓ Fe store in marrow
   E. ↓ Ferritin
9. A 29 year old woman was found to have a hemoglobin of 7.8 g/dl. with a reticulocyte count of 0.8%. The peripherial blood smear showed microcytic hypochromic anemia, Hemoglobin A2 and hemoglobin F levels were 2.4% and 1.3% respectively. The serum iron and the total iron binding capacity were 15 micro g/dl, and 420 micro g/dl, respectively. The most likely cause of anemia is:
   A. Iron deficiency anemia. *(AIIMS Nov 02)*
   B. Beta-thalassemia minor.
   C. Sideroblastic anemia.
   D. Anemia due to chronic infection.
10. Elevated serum ferritin, decreased serum iron and % transferring saturation are most consistent with the diagnosis of *(NBE)*
    A. Iron deficiency anemia
    B. Thalassemia
    C. Anemia of chronic disease
    D. Sideroblastic anemia
11. A child presents with hypochromic microcytic anemia, with normal levels of free Erythrocyte Protoporphyrin The most likely diagnosis is: *(AI 92)*
    A. Iron deficiency anemia
    B. Lead toxicity
    C. Thalassemia
    D. Anemia of chronic disease
12. A 16 year old young girl presents with a history of fatiguability weakness and lethargy. Complete Blood picture (CBC) reveals Haemoglobin of 7.0, MCV of 70, MCH of 20 pg/cell and Red cell Distribution Width (RDW) of 20. The most likely diagnosis is:
    A. Iron Deficiency Anemia *(AI 2010)*
    B. Thalassemia Minor
    C. Thalassemia Major
    D. Sickle cell trait
13. A student from Punjab presents for evaluation of anemia. His RDW was observed to be 13.5 while the MCV was 62.5 fl. The likely diagnosis is *(NBE)*
    A. Hemoglobin Punjab (HB-D Trait)
    B. Thalassemia Major
    C. Iron Deficiency Anemia
    D. Anemia of Chronic Disease

14. RDW is an indication of which of the following:
    A. Anisocytois *(NBE)*
    B. Poikilocytosis
    C. Macrocytosis
    D. Mirocytosis

15. A child has Hb-6.5 gm%, MCV-65, MCH-15 and protoporphyria with red cell distribution width much less is most likely to be suffering from :
    A. Thalassemia *(AIIMS June 2000)*
    B. Iron deficiency anaemia
    C. Porphyria
    D. Megaloblastic anaemia

16. A nine month old boy of Sindhi parents presented to you with complaints of progressive lethargy, irritability & pallor since 6 months of age. Examination revealed severe pallor. Investigation showed Hb-3.8 mg%; MCV-58 fl; MCH-19.4 pg/cell. Blood film shows osmotic fragility is normal (target cells and normoblasts). X-ray skull shows expansion of erythroid marrow. Which of the following is the most likely diagnosis? *(AI 2004)*
    A. Iron deficiency anemia
    B. Acute lymphoblastic anemia
    C. Hemoglobin D disease
    D. Hereditary spherocytosis

17. A 30 year old female being evaluated for anemia reveals the following indices: RBC count = 4.5 x 1012/L; MCV 55fl; TLC 8000. There is no history of blood transfusion. Which of the following is the most likely diagnosis: *(AIIMS Nov 2011)*
    A. Iron Deficiency Anemia
    B. Thalassemia major
    C. Thalassemia minor
    D. Megaloblastic anemia

18. Elevated serum ferritin, serum iron and percent transferrin saturation are most consistent with the diagnosis of : *(AI 2004)*
    A. Iron deficiency anemia
    B. Anemia of chronic disease
    C. Hemochromatosis
    D. Lead poisoning

19. Mentzer index more than 13 suggests a diagnosis of :
    A. Iron Deficiency Anemia *(NBE)*
    B. Thalassemia
    C. Hereditary Spherocytosis
    D. Autoimmune Hemolytic Anemia

## Iron Deficiency Anemia

20. All of the following are causes of iron deficiency anemia, Except: *(PGI June 01)*
    A. Chronic renal failure
    B. Celiac Sprue
    C. Hookworms
    D. Carcinoma colon

21. A patient with anemia has the following indices. MCV = 60; Hb = 5gm%; MCHC = 20. The most likely cause of his anemia is: *(PGI Dec 2000)*
    A. Phenytoin
    B. Blind loop syndrome
    C. Hookworm infectino
    D. CRF

22. Iron absorption is increased in all except:
    A. Iron deficiency *(PGI Dec 01, June 03)*
    B. Pregnancy
    C. Hypoxia
    D. Alkaline pH of stomach
    E. Ferrous iron salts

23. Which of the following findings is diagnostic of iron deficiency anemia : *(AI 2007)*
    A. Increased TIBC, decreased serum ferritin
    B. Decreased TIBC, decreased serum ferritin
    C. Increased TIBC, increased serum ferritin
    D. Decreased TIBC, increased serm ferritin

24. All of the following are features of iron deficiency anemia, except: *(AIIMS MAY 2013)*
    A. Increased RDW
    B. Decreased Serum Iron
    C. Decreased TIBC
    D. Decreased Serum Ferritin

25. Which of the following is true about Iron Deficiency Anemia *(NBE)*
    A. Increased Serum Ferritin
    B. Increased TIBC
    C. Increased Transferrin Saturation
    D. Macrocytic Hypochromic Anemia

26. The earliest sign of iron deficiency anaemia:
    A. Increase in iron binding capacity
    B. Decrease in serum ferritin level
    C. Decrease in serum iron level
    D. All the above *(AIIMS Feb 1997)*

27. Which of the following statements about iron deficiency anemia is true: *(NBE)*
    A. Decreased TIBC
    B. Increased Ferritin levels
    C. Bone marrow iron is decreased after serum iron is decreased
    D. Bone marrow iron is decreased earlier than serum iron

28. Most sensitive and specific test for diagnosis of iron deficiency is: *(AI 2003, AI 2001)*
    A. Serum iron levels
    B. Serum ferritin levels
    C. Serum transferrin receptor population
    D. Transferrin saturation

29. Best marker for iron deficiency is: *(NBE 2012)*
    A. Serum iron
    B. Serum ferritin
    C. Total Iron Binding capacity
    D. Transferrin saturation

30. The most suitable test to assess iron stores is:
    A. Serum iron *(NBE 2010)*
    B. Serum Ferritin
    C. TIBC
    D. Transferrin saturation

31. Which is not seen in Iron deficiency anaemia:
    A. Hyper-segmented neutrophils *(AI 2000)*
    B. Microcytosis preceeds hypochromia
    C. MCHC < 50%
    D. Commonest cause of anaemia in India

32. Which of the following is true about oral therapy for iron deficiency anemia: *(PGI Dec 05)*
    A. In 300 mg elemental iron given 100 mg get absorbed
    B. Reticulocytosis appears in one to 2 weeks and then peaks in 3-4 weeks
    C. Hemoglobin levels are usually corrected in six months of initiating therapy
    D. Decrease in absorption with improvement of symptoms
    E. Stop the Rx after normalizing the Hb

33. All of the following are indications of Intravenous Iron Administration, Except *(NBE)*
    A. Intermittent Gastrointestinal Blood Loss
    B. Iron Malabsorption
    C. Inability to Tolerate Oral Iron
    D. Patients on Erythropoietin Therapy

34. Iron Dextran Preparations may be used for all of the following conditions, except *(NBE)*
    A. Iron Deficiency anemia not responding to oral iron therapy
    B. Persistent blood loss
    C. Malabsorption related macrocytic anemia
    D. Patients on Erythropoietin for Anemia of chronic disease

35. Which of the following is associated with highest risk of Anaphylaxis *(NBE)*
    A. Iron Dextran
    B. Iron Sucrose
    C. Ferumoxytol
    D. Iron Gluconate

36. Iron overload occurs in all, *except* :
    A. Thalassemia *(AIIMS Sept 96)*
    B. Myelodysplastic syndrome
    C. Polycythemia vera
    D. Sideroblastic anaemia

## Anemia of Chronic Disease

37. Which of the following is true about Anemia of Chronic Disease: *(NBE)*
    A. Increased TIBC
    B. Normal serum iron levels
    C. Normal or increased serum ferritin
    D. Increased Transferrin saturation

38. A 25-year-old lady on treatment for Rheumatoid Arthritis has the following laboratory findings. Hemoglobin of 9 gm/dL; MCV-50 fl; Ferritin 200µg/L; TIBC 274 µg/dL; Serum iron 30µg/dL. What is the likely diagnosis: *(AIIMS Nov 2011)*
    A. Iron Deficiency Anemia
    B. Anemia of Chronic Disease
    C. Thalassemia Minor
    D. Autoimmune Hemolytic Anemia

39. All are true regarding Anaemia of Chronic Diseases, *except* : *(AIIMS 1999)*
    A. Decreased serum Fe
    B. Decreased Ferritin
    C. Decreased Total Fe Binding Capacity
    D. Increased Bone Marrow Fe

40. Seen in chronic inflammatory anemia is: *(PGI Dec 99)*
    A. Serum iron ↓, S. ferritin ↑ and transferrin ↓
    B. Serum iron ↑, S. ferritin ↑ and transferrin ↑
    C. Serum iron ↓, S. ferritin ↓ and transferrin ↑
    D. Serum iron ↑, S. ferritin ↓ and transferrin ↓

41. Which of the following is seen in chronic inflammatory anemia *(NBE)*
    A. Serum iron ↓ S. Ferritin ↑ and transferrin ↓
    B. Serum iron ↑ S. ferritin ↑ and transferrin ↑
    C. Serum iron ↓ S. ferritin ↓ and transferrin ↑
    D. Serum iron ↑ S. ferritin ↓ and transferrin ↓

42. True regarding anaemia of chronic disease are all *except* : *(AI 2000)*
    A. Decreased TIBC
    B. Increased macrophage iron in marrow
    C. Decreased serum ferritin level
    D. Decreased serum iron level

43. Anemia of chronic disease is characterized by all, except *(AIIMS May 94)*
    A. Decreased serum iron
    B. Increased total iron binding capacity (TIBC)
    C. Increased serum ferritin
    D. Increased macrophage iron in bone marrow

## Anemia of Chronic Renal Failure

44. All of the following are true about Anemia of chronic failure Except: *(PGI Dec 05)*
    A. Normocytic normochromic anaemia
    B. Erythropoietin improves the symptom
    C. Dialysis worsens anemia of renal failure
    D. Anemia is proportional to the kidney disease

45. Anemia in chronic renal failure (CRF) is due to:
    A. Decreased erythropoietin production
    B. Iron deficiency *(PGI June 01)*
    C. Hypoplastic bone marrow
    D. Decreased Vit B12
    E. Decreased folate levels

## Sideroblastic Anemia

46. Not present in Sideroblastic anaemia is :
    A. Microcytic anaemia *(AIIMS Feb 97)*
    B. Decreased transferrin saturation
    C. Sideroblast cells in blood smear film
    D. Ineffective erythropoiesis
47. A patient presents with increased serum iron, decreased TIBC, increased percent saturation and increased serum ferritin. Most probable diagnosis is :
    A. Anemia of chronic disease : *(AIIMS Nov. 2006)*
    B. Sideroblastic anemia
    C. Iron deficiency anemia
    D. Thalassemia minor

## Megaloblastic Anemia

48. Which of the following types of anemia is associated with a Raised MCV and Normal MCHC: *(AI 2012)*
    A. Sideroblastic anemia
    B. Vitamin B12 and Folic acid deficiency
    C. Beta thalassemia
    D. Iron deficiency anemia
49. Macrocytic anemia may be seen with all of the following conditions *except* :
    A. Liver disease *(AI 1998, AIIMS 1996)*
    B. Copper deficiency
    C. Thiamine deficiency
    D. Orotic aciduria
50. Megaloblastic anemia may be caused by all of the following *except* : *(AI 1997)*
    A. Phenytoin
    B. Methotrexate
    C. Pyrimethamine
    D. Amoxycilline
51. Megaloblastic anemia due to folic acid deficiency is commonly due to: *(AI 2006)*
    A. Inadequate dietary intake
    B. Defective intestinal absorption
    C. Absence of folic acid binding protein in serum
    D. Absence of glutamic acid in the intestine
52. Megaloblastic anemia in blind loop syndrome is due to: *(AI 99)*
    A. Vitamen $B_{12}$ malabsorption
    B. Bacterial overgrowth
    C. Frequent diarrhoea
    D. Decrease iron intake
53. Thiamine deficiency is known to occur in all of the following *except*: *(AI 2003)*
    A. Food Faddist
    B. Homocystinemia
    C. Chronic alcoholic
    D. Chronic heart failure patient on diuretics
54. Deficiency of the 'intrinsic factor of Castle' causes: *(NBE)*
    A. Microcytic anemia
    B. Pernicious anemia
    C. Cooley's anemia
    D. Aplastic anemia
55. Shilling's test is used to determine deficiency of *(NBE)*
    A. Vitamin B12
    B. Vitamin B6
    C. Folic Acid Deficiency
    D. Vitamin D Deficiency
56. Schilling's test may be used to establish a diagnosis of : *(NBE)*
    A. Intrinsic factor deficiency
    B. Pancreatic Endocrine dysfunction
    C. Megaloblastic anemia from folic acid deficiency
    D. All of the above
57. A patient has Hb 6gm%, folic acid 8 ng/ml, vitamin B12 60pg/ml, serum iron 160µg/dl, and MCV-104. The diagnosis is: *(AIIMS Nov 99)*
    A. Iron deficiency anemia
    B. Vitamin B12 deficinecy
    C. Folic acid deficiency
    D. Pyridoxine deficiency
58. A Patient presents with macroglossia and loss of tongue papilla. His Hb is 11.5 and MCV is 100. What should be the next step in investigating this patient?
    A. $B_{12}$ estimation *(AI 2008)*
    B. Brush biopsy of the lesion
    C. Fluconazole treatment
    D. Incision biopsy
59. Megaloblastic anemia should be treated with both folic acid vitamin $B_{12}$ because : *(AI 2008)*
    A. Folic acid alone causes improvement of hematologic symptoms but worsening of neurological symptoms
    B. It is a Co factor
    C. It is enzyme
    D. None of the above

# Hemolytic Anemias

## General Features

60. All of the following cause intravascular hemolysis, Except: *(NBE)*
    A. Mismatched Blood transfusion
    B. Snake bite
    C. Thalassemia
    D. Paroxysmal Nocturnal Hemoglobinuria (PNH)
61. Hemoglobinuria may be seen in all of the following conditions Except: *(NBE)*
    A. Mismatched Blood transfusion
    B. Paroxysmal cold hemoglobinuria
    C. Thermal burns
    D. Hereditary spherocytosis
62. Haemoglobinuria does not occur in :
    A. $CuSO_4$ poisoning *(AIIMS Feb 97)*
    B. Snake bite

C. Mismatched blood transfusion
D. Thalassemia

63. Haptaglobin levels are decreased in: *(AI 1996)*
A. A mismatched transfusion reactions
B. Thalassemia
C. G 6PD deficiency
D. All of the above

64. Chronic Hemolysis from which of the following conditions may be associated with iron deficiency:
A. Paroxysmal cold Haemoglobinuria *(AI 97)*
B. Thalassemia
C. Hereditary spherocytosis
D. G 6 PD deficiency

65. All of the following are features of hemolytic anemia Except: *(PGI June 04)*
A. Decreased RBC life span
B. Decreased Haptoglobin
C. Unconjugated hyperbilirubinemia
D. Bilirubin in urine
E. Altered Erythroid and Myeloid ratio

66. All are seen in Hemolytic anemia *except:*
A. Hemosiderinuria *(AI 1996)*
B. Reticulocytosis
C. Spherocytosis
D. Increased haptoglobin

67. Hemolytic anemia may be characterized by all of the following except- *(AIIMS May 05)*
A. Hyperbilirubinemia
B. Reticulocytosis
C. Hemoglobinuria
D. Increased plasma haptoglobin level

68. All are features of hemolytic anaemia except:
A. Thrombocytopenia *(AIIMS Dec 95)*
B. Hemosiderinuria
C. Decreased haptoglobin
D. Raised indirect bilirubin

69. Features seen in hemolytic anemia are all except:
A. Tear drop and Burr cells *(AIIMS May 07)*
B. ↓ Haptoglobin
C. Reticulocytosis
D. Hemoglobinuria

70. Reticulocytosis is NOT a feature of: *(AIIMS Dec 94)*
A. Paroxysmal nocturnal hemoglobinuria
B. Following acute bleeding
C. Hereditary spherocytosis
D. Anemia in CRF

71. Reticulocytosis is seen in all except: *(AIIMS May 07)*
A. P.N.H
B. Hemolysis
C. Nutritional anemia
D. Dyserythropoietic syndrome

72. Reticulocytosis is NOT a feature of *(AIIMS Dec 94)*
A. Paroxysmal nocturnal hemoglobinuria
B. Following acute bleeding
C. Hereditary spherocytosis
D. Anemia in CRF

73. Indirect Coomb's test detects: *(NBE)*
A. Antibodies attached to RBC Surface
B. Antibodies in the serum
C. Antigens attached to RBC Surface
D. Antigens in the serum

74. Direct Coomb's test detects: *(NBE)*
A. Antibodies attached to RBC Surface
B. Antibodies in the serum
C. Antigens attached to RBC Surface
D. Antigens in the serum

## Hereditary Spherocytosis

75. The following protein defects can cause hereditiary spherocytosis except : *(AI 07)*
A. Anykyrin
B. Palladin
C. Glycophorin C
D. Anion transport protein

76. Features of hereditary spherocytosis include all of the following *except* : *(AI.1998)*
A. ↑Osmotic fragility
B. ↑MCHC
C. ↑MCV
D. Decrease surface area per unit volume

77. Which of the following is not seen in Hereditary Spherocytosis: *(NBE)*
A. Direct Coomb's Positive
B. Increased Osmotic Fragility
C. Splenomegaly
D. Gall Stones

78. A patient with a positive family history of Anemia and Splenectomy in the family presents with abundant spherocytes in the peripheral blood. All of the following statement are true regarding his condition, except *(NBE)*
A. Coomb's test should be done to exclude immunological cause
B. Cholecystectomy may be required in future
C. Most common mode of inheritance is Autosomal Recessive
D. Splenectomy may be required

79. Usually associated with parvovirus B19 infection in those with hereditary spherocytosis:
A. Mild to moderate splenomegaly
B. Aplastic crisis *(NBE)*
C. Gallstones
D. Hemolytic Crisis

80. Aplastic anemia in hereditary spherocytosis precipitated by- *(PGI Dec 05)*
A. Parvo virus
B. HIV
C. Adenovirus
D. Influenza virus
E. Measles virus

81. With regards to hereditary spherocytosis, which of the following is FALSE? *(NBE)*
   A. Usually has autosomal dominant inheritance
   B. Caused by mutations in genes for proteins such as spectrin, ankrin or band 3
   C. Red blood cells are destroyed in the spleen
   D. Aplastic crises are common

82. Osmotic fragility is increased in: *(PGI June 98)*
   A. Sickle cell anemia
   B. Thalassemia
   C. Hereditary spherocytosis
   D. Chronic lead poisoning

83. Decreased osmotic fragility is seen in (select two options): *(PGI Dec 2000)*
   A. Herediatry spherocytosis
   B. Sickle cell ds
   C. Autoimmune hemolytic anemia
   D. Thallasemia

84. Splenectomy is most useful in : *(AI 1998)*
   A. Thrombocytopenia
   B. Hereditary spherocytosis
   C. H.S. purpura
   D. Sickle cell anemia

85. All of the following are true regarding Splenectomy in patients with Hereditary Spherocytosis, Except *(NBE)*
   A. Avoid in mild cases
   B. Delay Splenectomy until at least 4 years old age
   C. Anti-pneumococcal Vaccination must be given before splenectomy
   D. Prolonged Anti-pneumococcal Antibiotic Prophylaxis must be given after splenectomy

## G6 PD Deficiency

86. With regards to G6PD deficiency, which of the following is FALSE? *(NBE)*
   A. Affects the pentose phosphate pathway
   B. Associated with neonatal jaundice
   C. Acute haemolysis can be precipitated by broad beans
   D. X-linked recessive disorder that does not affect heterozygous females

87. All of the following statements about genetics of G6PD Deficiency are true, except:
   A. X-linked Inheritance *(NBE)*
   B. More severe in Men
   C. Contradicts Lyon Hypothesis
   D. May affect Heterozygous Females

88. Chronic Non – Spherocytic Hemolytic Anemia is seen in which class of G6PD Deficiency:
   A. Class I *(NBE)*
   B. CLASS II
   C. Class III
   D. Class IV

89. Hemolysis in G6PD may be caused by all Expect:
   A. Primaquine *(AI 2008)*
   B. Chloroquine
   C. Pyrimethamine
   D. Quinine

90. Which doesn't cause hemolysis in G6 PD deficiency:
   A. Oestrogen *(PGI Dec 99)*
   B. Salicylates
   C. Primaquine
   D. Nitrofurantoin

91. Primaquine may cause hemolysis in :
   A. G-6-PD deficiency *(AI 1998)*
   B. NADP-deficiency
   C. Methemoglobin reductase deficiency
   D. Crabb's disease

## Hemoglobinopathies: Sickle Cell Anemia

92. The primary defect which leads to sickle cell anemia is- *(NBE)*
   A. An abnormality in porphyrin part of hemoglobin
   B. Replacement of glutamate by valine in B-chain of HbA
   C. A nonsense mutation in the B-chain of HbA
   D. Substitution of valine by glutamate in the A chain of HbA

93. Which of the following is not seen in a chronic case of Sickle cell anemia : *(AI 1996)*
   A. Hepatomegaly
   B. Pulmonary hypertension
   C. Cardiomegaly
   D. Splenomegaly

94. All are true for sickle cell anemia, *except*
   A. Pulmonary arterial hypertension
   B. Fish vertebra *(AIIMS May 94)*
   C. Leukopenia
   D. Increased size of heart

95. All of the following statements are true about sickle cell disease *except* *(AI 2004)*
   A. Patient may require frequent blood transfusions
   B. Acute infection is the most common cause of mortality before 3 years of age.
   C. There is positive correlation between conc. HBS and polymerization of HBS.
   D. Patient presents early in life before 6 months of age.

96. All of the following are true about sickle cell disease, except: *(PGI June 2008)*
   A. Mutation in α chain
   B. Symptoms ameliorated by HbF
   C. Venoocclusive cries is cause of morbidity
   D. Bone pain is presenting feature

97. Commonest acute presentation of sickle cell anaemia is: *(AIIMS Dec 98)*

A. Priapism
B. Bone pain
C. Fever
D. Splenomegaly.

98. Heterozygous sickle cell anemia gives protection against: *(AI 2010)*
A. G6PD
B. Malaria
C. Thalassemia
D. Dengue fever

99. Which of the following is not seen on hemoglobin electrophoresis in sickle cell anemia: *(AI 2001)*
A. HbA
B. HbA2
C. HbF
D. HbS

100. Sickle cell trait patient do not have manifestations as that of Sickle cell disease, because : *(AIIMS 2001)*
A. 50% HbS is required for occurrence of sickling
B. HbA prevents sickling
C. HbS is less than 50% & HbA has low affinity for HbS
D. HbA prevents polymerization of Hbs

101. The mother has sickle cell disease; Father is normal; Chances of children having sickle cell disease and sickle cell trait respectively are : *(AI 2001)*
A. 0 and 100%
B. 25 and 25%
C. 50 and 50%
D. 10 and 50%

102. Crew haircut appearance in X-rays skull and Gandy gamma bodies are seen in- *(AIIMS Nov 93)*
A. G6-PD deficiency
B. Hodgkin's lymphoma
C. Hereditary spherocytosis
D. Sickle cell anaemia

103. Sickle cell Anemia leads to resistance towards *(DNB Dec 2009)*
A. P. Falciparum
B. P. Ovale
C. P. Malariae
D. P. Vivax

## Hemoglobinopathies: Thalassemias

104. Which of the following is a Quantitative defect in globin synthesis: *(NBE)*
A. Thalassemia
B. Sickle Cell Hemoglobinopathy
C. G6PD Deficiency
D. Diamond-Blackfan Syndrome

105. In Beta thalassemia, there is : *(AIIMS May 01)*
A. Increase in beta chain, decrease in alpha chain
B. Decrease in beta chain, increase in alpha chain
C. Decrease in beta chain, decrease in alpha chain
D. Increase in beta chain, increase in alpha chain

106. The most common mulations in Beta thalassemia involves: *(NBE)*
A. Intron-1
B. Intron-22
C. 619 bp deletion
D. 3.7 bp deletion

107. A 25-year female presented with mild pallor and moderate hepatosplenomegaly. Her hemoglobin was 92 dl/L and fetal hemoglobin level was 65%. She has not received any blood transfusion till date. She is most likely to be suffering from: *(AIIMS Nov 02)*
A. Thalassemia major
B. Thalassemia intermedia.
C. Hereditary persistent fetal hemoglobin, homozygous state.
D. Hemoglobin D, homozygous state.

108. A 21 year old male presents to the emergency department with sever anemia and haemoglobin levels of 5 gm/dl. He gives a history of similar presentation in the past which wave adequately managed by a single blood transfusion. He has not required any further blood transfusions till date. Most probable diagnosis is: *(NBE)*
A. Thalassemia major
B. Thalassemia Minor
C. Thalassemia intermedia
D. Autoimmune hemolytic anemia

109. A 23 years old asymptomatic female pilot has MCV-70, ferritin – 100g/L, Hb-10gm%, what is the cause:
A. Thalassemia trait *(AI 2009)*
B. $B_{12}$ def
C. Folate def
D. Iron def

110. All of the following are true about β thalassemia trait, Except: *(PGI June 2008)*
A. Microcytic hypochromic picture
B. ↑ed HbA2
C. ↑ed HbF
D. Patient requires blood transfusion

111. All are true about β - thalassemia trait Except:
A. ↑ HbF *(PGI June 04)*
B. ↑$HbA_2$
C. Microcytosis
D. Severe anaemia

112. The most important diagnostic feature for beta thalassaemia trait: *(NBE)*
A. raised HbF
B. reduced MCH
C. reduced MCV
D. raised HbA2

113. True about α-thalassemia trait : *(PGI June 06)*
A. Increased HbF
B. Increased HbA2
C. Microcytosis
D. Severe anemia

114. A 32-year-old female, asymptomatic, not requiring blood transfusion, presents with Hb 13.0 gm/dl. Her HbF levels are 95%, Hb $A_2$ 1.5%. Which of the following is the most likely diagnosis *(AIIMS May 04)*
   A. Hereditary persistence of fetal hemoglobin
   B. Beta homozygous thalassemia
   C. Thalassemia intermedia
   D. Beta heterozygous thalassemia

115. A child aged 2 year presents with nonspecific symptoms suggestive of anemia. On peripheral blood smear target cells are seen. He has hypochromic mic-zrocytic picture and Hb of 6 gm. He also has 'a positive family history' Next investigation of choice is *(AI 01)*
   A. Hb electrophoresis
   B. Coombs test
   C. Liver function tests
   D. Osmotic fragility test

116. The peripheral blood smear of a patient shows features of thalassemia, also presented with anaemia. Family history is also +ve. The investigation done to establish the diagnosis is: *(AIIMS 1999)*
   A. ESR estimation
   B. Blood spherocyte estimation
   C. Bone marrow aspiration
   D. Hb-electrophoresis

117. Diagnosis of beta Thalassemia is established by:
   A. NESTROFT Test.
   B. Hb $A_1$ C estimation.
   C. Hb electrophoresis.
   D. Target cells in peripheral smear.

118. NESTROFT test is used for screening of : *(NBE)*
   A. Thalassemia
   B. Autoimmune Haemolytic Anaemia
   C. Hereditary Spherocytosis
   D. G6PD Deficiency

119. A 5 year old girl came with history of progressively increasing pallor since birth and hepatosplenomegaly. Which of the following is the most relevant test for achieving diagnosis : *(AI 2004)*
   A. Hb electrophoresis
   B. Peripheral smear examination
   C. Osmotic fragility test
   D. Bone marrow examination

120. Hair on end appearance is seen in X-rays skull in:
   A. Thalassemia *(AIIMS June 97)*
   B. Hydrocephalus
   C. Chronic malaria
   D. Sickle cell analuria

121. Deletion of one alpha globin gene on one chromosome is best defined as: *(NBE)*
   A. Hb Barts hydrops fetails
   B. Alpha thalassaemia major
   C. Alpha thalassaemia trait
   D. Alpha Thalassemia silent carrier

122. Which of the following is caused by deletion of all four alpha globin genes: *(NBE)*
   A. Beta thalassemia major
   B. Hb Barts
   C. HbH
   D. $\alpha^{\circ}$ thalassemia trait

123. HbH is characterized by: *(NBE)*
   A. Deletion of three alpha genes
   B. Deletion of three alpha and one beta gene
   C. Deletion of two alpha and two beta genes
   D. Deletion of four alpha genes

124. Which of the following represent Fetal Haemoglobin (HBF) *(NBE)*
   A. Alpha 2 Beta 2
   B. Alpha 2 Gamma 2
   C. Alpha2 delta 2
   D. Delta 4

125. Hemoglobin Portland is best defined as:
   A. Alpha 2 ; Delta 2 *(NBE)*
   B. Alpha 2 ; Epsilon 2
   C. Zeta 2 ; Gamma 2
   D. Zeta 2 ; Epsilon 2

126. Haemoglobin F is raised in: *(AIIMS Dec 97)*
   A. Juvenile chronic myeloid leukemia
   B. Hereditary spherocytosis
   C. Congenital red cell aplasia
   D. Mysthania gravis

127. HbA2 levels are increased in all Except:
   A. Alpha Thalassemia *(PGI June 02)*
   B. Beta Thalassemia
   C. Sickle cell anemia
   D. Megaloblastic Anemia
   E. Hyperthyroidism
   E. anaemia

128. Which of the following is NOT used for iron chelation in thalassemia patients?
   A. Kelfer *(NBE)*
   B. Desferal
   C. Deferiprone
   D. Penicillamine

## Autoimmune Hemolytic Anemia

129. Warm autoimmune hemolytic anaemia may be seen in all of the following conditions *except* : *(AI 1997)*
   A. Systemic lupus erythematous
   B. $\alpha$-Methyl dopa therapy
   C. Non hodgkin's lymphoma
   D. Mycoplasma pneumonia

130. Cold haemagglutinin is associated with- *(AI 97)*
   A. Anti IgM
   B. Anti IgG
   C. Anti IgA
   D. Donath landsteiner antibody

131. Autoimmune hemolytic anemia is seen in
A. Sickle cell anemia *(AIIMS May 94)*
B. Chronic lymphocytic leukemia (CLL)
C. Acute myelocytic leukemia (AML)
D. Multiple myeloma

132. Autoimmune hemolytic anemia is associated with malignancy of which lineage : *(AI 2007)*
A. T cell
B. B cell
C. Pre B cell
D. Pre T cell

133. Autoimmune haemolytic anemia is seen in:
A. ALL *(AI 2001)*
B. AML
C. CLL
D. CML

134. Coomb's +ve Hemolytic Anaemia is seen in *except* :
A. Alcoholic cirrhosis *(AI 2000)*
B. Chronic active hepatitis
C. Primary biliary cirrhosis
D. Primary sclerosing cholangitis

135. Coombs positive hemolytic anemia associated with:
A. TTP *(AI 2009)*
B. PAN
C. SLE
D. HUS

136. All of the following conditions are associated with coombs positive hemolytic anemia Except *(AI 2009)*
A. Thrombatic Thrombocytopenic purpura (TTP)
B. Scleroderma
C. SLE
D. PAN

137. Which of the following conditions is associated with Coomb's positive hemolytic anaemia:
A. Thrombotic thrombocytopenic purpura.
B. Progressive systemic sclerosis. *(AIIMS May 03)*
C. Systemic lupus erythematosus.
D. Polyarteritis nodosa

138. A 20 years old female presenting with anemia, mild jaundice for 2 years, peripheral smear showing spherocytes, the best investigation to be done is:
A. Reticulocyte count *(AIPGMEE 08)*
B. Osmotic fragility test
C. Coombs test
D. Bone marrow aspiration

139. A 23 Year old female presents with anemia and jaundice for 2 years. Peripheral smear shows spherocytes. The best investigation to be done is :
A. Reticulocyte Count *(AIIMS Nov. 2006)*
B. Osmotic Fragility Testing
C. Coombs Test
D. Bone Marrow Aspiration

140. Anaemia due to antibodies against blood group antigens: *(NBE)*
A. Hereditary spherocytosis
B. G6PD deficiency
C. Haemolytic disease of the newborn
D. Alpha thalassaemia major

141. A positive direct anti-globulin (Coombs) test indicates: *(NBE)*
A. Congenital red cell aplasia
B. Hereditary spherocytosis
C. Haemolytic disease of the newborn
D. G6PD deficiency

142. 33. Which of the following is an immune response cause of anaemia? *(NBE)*
A. Diamond Blackfan anaemia
B. Hereditary spherocytosis
C. Glucose-6-phosphate dehydrogenase deficiency
D. Haemolytic disease of the newborn

## Microangiopathic Hemolytic Anemia

143. All of the following are causes of fragmented RBC in peripheral blood Except: *(PGI June 05, 02)*
A. Microangiopathic hemolytic anemia
B. D.I.C
C. Hemophilia-A
D. Malignant hypertension
E. HELLP syndrome

144. A 25-year-old pregnant lady presents with thrombocytopenia (Platelet count < 50,000) and fragmented RBC's in peripheral smear. Which of the following is the least likely differential diagnosis? *(AI 2012)*
A. Thrombotic Thrombocytopenic Purpura (TTP)
B. Disseminated Intravascular Coagulation (DIC)
C. HELLP syndrome
D. Evan's syndrome

145. The differential diagnosis of micro-angiopathic anemia includes all Except: *(PGI Dec. 05)*
A. Sepsis
B. Hemolytic uremic syndrome
C. MI
D. Eclampsia
E. Scleroderma

146. Microangiopathic Hemolytic anemia is seen in all Except: *(AIIMS Nov 2009)*
A. TTP
B. Metallic heart valve
C. Microscopic polyangitis
D. Anti-phospholipid syndrome

147. Microangiopathic hemolytic anemia is seen in all Except:
A. HUS *(PGI June 01, 00)*
B. ITP

C. Malignant hypertension
D. Prosthetic valves
E. TTP

148. Schistocytes are seen in: *(NBE)*
A. Aplastic anemia.
B. Megaloblastic anemia.
C. Iron deficiency anemia.
D. Microanglopathic hemolytic anemia

## Proxysmal Nocturnal Hemoglobinuria (PNH)

149. PNH is associated with all of the following conditions, *except* : *(AI 2002)*
A. Aplastic anemia
B. ↑ed LAP scores
C. Venous thrombosis
D. Iron deficiency anemia

150. All of the following can be associated with PNH Except: *(AI 2009)*
A. Cerebral thrombosis
B. Budd chiari syndrome
C. Pancytopenia
D. Massive splenomegaly

151. All are true regarding paroxysmal nocturnal haemoglobinuria, *except*: *(AIIMS Dec 91)*
A. Haemosiderinuria
B. Pancytopenia
C. Increased alkaline phosphatase
D. Cellular marrow

152. A stem cell disorder affecting all the three cell lines platelets, RBCs and leucocytes is : *(AIIMS May 01)*
A. Hemolytic anaemia
B. Paroxysmal cold haemoglobinuria
C. Paroxysmal nocturnal haemoglobinuna
D. Blackfan Diamond syndrome

153. All of the following are true about PNH, Except:
A. Hypocellular marrow *(PGI Dec 2000)*
B. Budd-chirai syndrome
C. Thrombosis
D. LAP score low

154. Which of the following is NOT seen in Paroxysmal Nocturnal Hemoglobinuria : *(AIIMS Nov. 2000)*
A. Thrombosis
B. Hemosiderinuria
C. Decreased LDH
D. Thrombocytopenia

155. PNH is associated with a deficiency of : *(AI 2010)*
A. DAF
B. MIRL
C. GPI Anchored protein
D. All of the above

156. PNH is associated with deficiency of: *(AI 2010)*
A. DAF (Decay accelerating factor)
B. MIRL (Membrane inhibitor of reactive lysis)
C. GPI Anchored Proteins (Glycosyl phosphatidyl Inositol anchored proteins)
D. LFA (Lymphocyte function associated antigen)

157. HAM test is based upon : *(AIIMS Nov06)*
A. GPI Anchor Proteins
B. Complement
C. Spectrin protein
D. Mannose binding proteins

158. The gold standard test for the diagnosis of Paroxysmal Nocturnal Hemoglobinuria (PNH) is:
A. Flow cytometry *(NBE)*
B. Sucrose hemolysis test
C. HAM test
D. Genetic testing

# Aplastic Anemia and Myelodysplastic Syndrome

## Aplastic Anemia and Pancytopenia

159. All the following are examples of diseases causing Aplastic anemia *except* : *(AI 1995)*
A. PNH
B. Hepatitis
C. Pregnancy
D. Cold hemoglobinuria

160. Aplastic anemia is seen in all of the following except:
A. PNH *(PGI Dec 03)*
B. Chloramphenicol
C. Hepatitis A
D. HIV-1
E. Parvovirus

161. Pancytopenia with cellular marrow is seen in:
A. PNH *(AI 2007)*
B. G6PD deficiency
C. Acquired aplastic anemia
D. Thalassemia

162. Pancytopenia with hypercellular marrow may be seen due to all of the following except: *(NBE)*
A. Myelodysplasia
B. Paroxysmal Nocturnal Hemoglobinuria
C. Dyskeratosis congenita
D. Sarcoidosis

163. Which of the following causes of Anemia is associated with a Hypoplastic marrow: *(AI 2012)*
A. Fanconi's Anemia
B. Paroxysmal Nocturnal Hemoglobinuria (PNH)
C. Hypersplenism
D. Myelofibrosis

164. Pancytopenia with hypercellular bone marrow is seen in: *(AI 2007)*
A. PNH
B. Megaloblastic anemia
C. Acquired aplastic anemia
D. Thalessemia

165. Pancytopenia with Cellular marrow is seen in all except : *(AIIMS Nov. 2006)*
   A. Megaloblastic Anemia
   B. Myelodysplasia
   C. PNH
   D. G6PD Deficiency

166. Pancytopenia with a cellular marrow is seen in all except: *(AIIMS Nov 07)*
   A. PNH
   B. Megaloblastic anemia
   C. Myelodysplastic syndrome
   D. Dyskeratosis congenital

167. All of the following are causes of pancytopenia with cellular bone marrow except: *(NBE)*
   A. Paroxysomal noctural hemoglobinuria
   B. Dyskeratosis congenita
   C. Megaloblastic anemia
   D. Hairy cell leukemia

168. Pancytopenia with cellular marrow is seen in all Except: *(AI 2008)*
   A. Megaloblastic anemia
   B. Myelodysplasia
   C. Paroxysmal nocturnal hemoglobinuria
   D. G6 PD deficiency

169. Vasanti, a 25-year-old-girl, presents with complaints of fever and weakness. On examination there is splenomegaly of 3 cm below the costal margin. Hb is 8 gm/dL, TLC is 3,000/$mm^3$, platelet count is 80,000/$mm^3$. Which of the following is the least likely diagnosis : *(AIIMS Nov. 2000)*
   A. Acute lymphocytic leukemia
   B. Anemia of chronic disease
   C. Aplastic anemia
   D. Megaloblastic anemia

170. The most common inherited form of aplastic anaemia: *(NBE)*
   A. Fanconi anaemia
   B. Schwachman-Diamond syndrome
   C. Diamond-Blackfan anaemia
   D. Dyskeratosis Congenita

171. All of the following statements about Fanconi's anemia are true, Except. *(AI 2010)*
   A. Autosomal dominant inheritance
   B. Hypocellular Bone Marrow
   C. Congenital Anomalies
   D. Usually normocytic / macrocytic cell morphology

172. Aplastic Anemia with skeletal abnormalities, short stature and pancreatic exocrine failure suggests a diagnosis of: *(NBE)*
   A. Fanconi anaemia
   B. Diamond-Blackfan anaemia
   C. G6PD deficiency
   D. Schwachman-Diamond syndrome

173. All of the following conditions may be associated with Pancytopenia and Splenomegaly, Except :
   A. Aplastic Anemia *(NBE)*
   B. Hairy Cell Leukemia
   C. Myelofibrosis
   D. Hypersplenism

174. True about aplastic anemia is all Except:
   A. Splenomegaly *(PGI June 05)*
   B. Reticulocytopenia
   C. Thrombocytopenia
   D. Neutropenia

175. A pt with an Hb of 6, WBC count of 2000, has a normal Different count except for having 6% blasts; platelets are reduced to 80,000; moderate splenomegaly is present; possible diagnosis is:
   A. Leukemia *(AI 2001)*
   B. Aplastic anemia
   C. Hemolysis
   D. ITP

176. A patient aged 63 years, is diagnosed to have severe aplastic anemia. HLA compatible sibling is available. The best option of treatment is : *(AIIMS May. 06)*
   A. Anti-thymocyte globulin followed by cyclosporine
   B. A conventional bone marrow transplantation from the HLA identical sibling
   C. A non-myeloablative bone marrow transplantation from the HLA identical sibling
   D. Cyclosporine

177. A 20 yrs adult presents with severe hypoplastic anemia. What is most effective treatment :
   A. α-interferon *(AI 2002)*
   B. IL-2
   C. ATG therapy
   D. Bone marrow transplantation

**Myelodysplastic Syndrome**

178. Ring sideroblasts are characteristically seen in:
   A. Myelodysplastic syndrome (MDS) *(AI 2008)*
   B. Acute Lymphoid Leukemia (ALL)
   C. Acute Myeloid Leukemia (AML)
   D. Anemia of chronic disease

179. Pawn ball megakaryocytes are characteristic of:
   A. Myelodysplastic syndrome *(NBE Pattern14-15)*
   B. Idiopathic thrombocytopenic purpura
   C. Thrombotic thrombocytopenic purpura
   D. Chloramphenicol toxicity

180. In which of the following age group myelodysplastic syndrmome (MDS) are most common: *(AI 06)*
   A. 2-10
   B. 15-20
   C. 5q
   D. >50

181. Which is the most common cytogenetic abnormality in adult myelodysplastic syndrome (MDS) - *(AI 04)*
A. Trisomy 8
B. 20q-
C. 5q-
D. Monosmy 7

## Myeloproliferative Disorders

### General/Classification

182. Which of the following is NOT a myeloproliferative disease: *(AIIMS Nov. 2000)*
A. Polycythemia rubra vera
B. Acute myeloid leukemia
C. Chronic myeloid leukemia
D. Essential thrombocytosis

183. A patient with Myeloproliferative syndrome presents with decreased while cell count and decreased platelets. The most likely diagnosis is: *(AI 1993)*
A. Chronic myeloid leukemia
B. Myelofibrosis
C. Polycythemias vera
D. Essential thrombocytosis

184. Massive Splenomegaly is least likely to be associated with which of the following Myeloproliferative disorders: *(AI 2012)*
A. Chronic Myeloid Leukemia (CML)
B. Polycythemia Vera (PV)
C. Essential Thrombocytosis (ET)
D. Primary Myeloproliferative (PMF)

185. Laboratory evaluation for the differential diagnosis of chronic myeloproliferative disorders includes all the following except- *(AIIMS Nov 04)*
A. Chromosomal evaluation
B. Bone marrow aspiration
C. Flow-cytometric analysis
D. Determination of red blood cell mass

186. Laboratory evaluation for the differential diagnosis of chronic myeloproliferative disorders includes all the following *except* : *(AIIMS Nov.2004)*
A. Chromosomal evaluation
B. Bone marrow aspiration
C. Flow-cytometric analysis
D. Determination of red blood cell mass

187. Polycythemia is typically associated with the following haematocrit values *(NBE)*
A. 60% in Men; > 55% in Women
B. 60% in Women; > 55% in Men
C. 55% in Men; > 50% in Women
D. 50% in Women; > 55% in Men

### Polycythemia

188. All of the following are the causes of relative polycythemia *except*: *(AI 2005)*
A. Dehydration.
B. Dengue haemorrhagic fever.
C. Gaisbock syndrome.
D. High altitude.

189. Gaisbock syndrome is known as *(NBE)*
A. Primary Familial Polycythemia
B. High Altitude Erythrocytosis
C. Spurious Polycythemia
D. Polycythemia Vera

190. A 59-year-old male came with Hb 18.0 gm/dl on three occasions. The resident doctor wants to exclude Polycythemia Vera. Which of the following is the most relevant investigation : *(AIIMS May 04)*
A. Hematocrit
B. Total leukocyte count
C. Red cell mass
D. Reticulocyte count

191. Secondary Polycythemia may be seen in:
A. Cor pulmonale *(NBE)*
B. Congestive cardiac failure
C. Acyanotic congenital heart disease
D. All of the above

192. Monge's disease refers to: *(NBE)*
A. Primary Familial Polycythemia
B. High Altitude Erythrocytosis
C. Spurious Polycythemia
D. Polycythemia Vera

193. Which of the following factors can differentiate primary polycythemia from secondary polycythemia.
A. Increased Red cell mass *(NBE)*
B. Arterial oxygen tension <90% on room air
C. Pruiritis
D. Hypertension

194. Erythropoietin is increased in all except: *(NBE)*
A. Hepatocellular carcinoma
B. Renal cell carcinoma
C. Cerebellar Hemangioblastoma
D. Pancreatic carcinoma

195. Which of the following is not commonly seen in Polycythemia Vera ? *(AI 2002)*
A. Thrombosis
B. Hyperuricemia
C. Prone for acute leukemia
D. Spontaneous severe infection

196. True about polycythemia rubra vera is all Except:
A. Bleeding *(PGI Dec 97)*
B. Thrombosis
C. ↓ed ESR
D. Infection

197. In Polycythemia vera, all the following are seen *except*: *(AIIMS May 01)*
   A. Thrombocytopenia
   B. Increased GI bleed
   C. Thrombosis
   D. Transient visual loss
198. All of the following are seen in polycythemia rubra vera *except*: *(AIIMS Nov. 2000)*
   A. Increased Vit $B_{12}$ binding capacity (>9000 micromols/dL)
   B. Decreased LAP Score
   C. Leucocytosis
   D. Increased platelets
199. Which of the following is a major criteria for diagnosis of poycythemia vera: *(AI 2010)*
   A. Presence of JAK-2 mutation
   B. Low Erythropoetin levels
   C. High Leucocyte Alkaline Phosphatase (↑LAP score)
   D. Thrombocytosis
200. Which is not seen in polycythemia vera :
   A. Increased Vit $B_{12}$ binding capacity
   B. Increase erythropoietin level
   C. Increase RBC count *(AIIMS Feb 97)*
   D. Ocular congestion
201. Tumor associated with polycythemia is :
   A. Sarcoma *(AI 2001, AI 1995)*
   B. Pituitary adenoma
   C. Cerebellar haemangioblastoma
   D. None of the above.

## Myelofibrosis

202. A patient has the following findings-splenomegaly, low RBC count, normal WBC, and platelet count and peripheral blood smear shows tear drop cells. Repeated BM aspiration is unsuccessful. The probable diagnosis is: *(AIIMS 1999)*
   A. Thalassemia
   B. Chronic myeloid leukemia
   C. Iron deficiency anaemia
   D. Myelofibrosis
203. A pt. being investigated for anemia has a dry marrow tap; peripheral smear reveals tear drop cells; likely diagnosis is: *(AI 2001)*
   A. Leukemia
   B. Lymphoma
   C. Myelofibrosis
   D. Polycythemia rubra vera
204. Leukoerythroblastic picture may be seen in all of the following, *except*: *(AI 2003)*
   A. Myelofibrosis
   B. Metastatic carcinoma
   C. Gaucher's disease
   D. Thalassemia

## Essential Thrombocytosis

205. A 45 year old female patient presents with symptoms of easy bruisability and frequent headaches. Physical examination show a moderate splenomegaly. Blood counts shows a normal leucocyte count and a platelet count of $1000 \times 10^3$/cu mm. The leucocyte alkaline phosphatase score is normal. Which one of the following is the drug of choice for the treatment of this patient? *(AIIMS Nov 03)*
   A. Hydroxyurea
   B. Radioactive phosphorus
   C. Anagrelide
   D. Interferon alpha
206. A patient presents with a platelet count of 700 x 109/L with abnormalities in size, shape and granularity of platelets. WBC count is 12 x 109/L, hemoglobin is 11g/dl and Philadelphia chromosome is absent. The most likely diagnosis would be:
   A. Polycythemia vera *(AIIMS May. 2006)*
   B. Essential thrombocythemia
   C. Chronic myeloid leukemia
   D. Leukemoid reaction

# Lymphomas & Chronic Leukemias

## Hodgkin's Lymphoma

207. The subtype of Hodking's disease, which is histogentically distinct from all the other subtypes, is-
   A. Lymphocyte predominant *(AI 05)*
   B. Nodular sclerosis
   C. Mixed cellularity
   D. Lymphocyte depleted
208. Cells characteristic of Hodgkin's disease are: *(NBE)*
   A. Lacunar cells
   B. Red-Stemberg cells
   C. Giant cells
   D. Eosinophils
209. The lymphocytic and histiocytic variant of Reed-Sternberg cell is seen in: *(AIIMS Nov 05)*
   A. Follicular center lymphoma
   B. Lymphocyte depleted Hodkin's disease
   C. Nodular sclerosis Hodkin's disease
   D. Lymphocyte predominant Hodkin's disease
210. Hodgkin's lymphoma of the nodular subtype is associated with: *(AIIMS June 1992)*
   A. Lacunar cells
   B. Popcorn cells
   C. Reticular variant
   D. None of the above
211. Most common type of Hodgkin's lymphoma is :
   A. Nodular sclerosis *(AI 1996)*
   B. Lymphocyte predominance
   C. Mixed cellularity
   D. Lymphocyte depletion

212. Most common type of hodgkin's lymphoma in India is : *(AI 1998)*
A. Nodular sclerosis
B. Lymphocyte predominance
C. Mixed nodulatory
D. Lymphocyte depletion

213. Which of the following types of Hodgkins lymphomas is associated with a good prognosis *(NBE)*
A. Lymphocyte Predominance
B. Lymphocyte Depletion
C. Nodular sclerosis
D. Mixed cellularity

214. Best prognostic type of Hodgkin's lymphoma is :
A. Lymphocytic predominant *(AIIMS June 1998)*
B. Lymphocytic depletion
C. Mixed cellularity
D. Nodular sclerosis

215. Classical markers for Hodgkin's disease is-
A. CD 15 and CD 30 *(AIPGMEE 08)*
B. CD 15 and CD 22
C. CD 15 and CD 20
D. CD 20 and CD 30

216. Diagnosis of Hodgkins disease is based on all of the following, except: *(PGI Dec 1999)*
A. Reed- Sternberg cells
B. Reactive cellular background
C. Atypical cells in backgriound
D. CD 30 positivity

217. All are true regarding Hodgkin's lymphoma, *except* :
A. CNS is the commonest site of involvement
B. Characteristic cell is a Reed Sternberg cell
C. Mediastinal involvement is common in nodular--sclerosis type. *(AI 2000)*
D. Eosinophils, plasma cells and neutrophils increase.

218. Most common lymph node involved in Hodgkin's lymphoma is *(NBE)*
A. Inguinal
B. Cervical
C. Axillary
D. Sub-clavicular

219. The paraneoplastic syndrome associated with Hodgkin's disease is : *(AIIMS Nov. 05)*
A. Nephrotic syndrome
B. Retinopathy
C. Cerebellar degenerative disease
D. Acanthosis nigricans

220. All of the following are the good prognostic features Hodgkin's disease except: *(AI 04)*
A. Haemoglobin>10 gm/dl
B. WBC count<15000/mm3
C. Absolute lymphocyte count<600/ul
D. Age < 45 yrs

221. All of the following are poor prognostic factors for Hodgkin's disease, Except: *(PGI Dec 01)*
A. Younger age
B. Systemic manifestations
C. Lymphocyte depletion
D. Mediastinal disease
E. Stomach involvement

222. A patient presents to the hospital for percistant fever and significant weight loss for the post two months. On examination he is observed to have cervical and axillary lymphadenopathy. Other examination and investigations are unremarkable. Biopsy from the cervical nodes is performed and returns positive for Hodgkin's Lymphoma. The patient can be staged as haring:
A. Stage II A *(AI 1997)*
B. Stage II B
C. Stage II A
D. Stage II B

223. A patient with Hodgkin's lymphoma is having a single cervical lymphnode. Biopsy showed lymphocyte predominant variant. Which of the following is the treatment of choice:
A. Chemotherapy with Radiotherapy
B. Chemotherapy only *(AIIMS Nov 2000)*
C. Radiotherapy only
D. No treatment needed

224. A patient with Hodgkin's lymphoma presents with isolated cervical lymphadenopathy. Biopsy from the lesion shows characteristic lacunar cells. The treatment of choice for this patient is: *(NBE)*
A. Chemotherapy with Radiotherapy
B. Chemotherapy alone
C. Radiotherapy alone
D. No treatment needed

225. True for Hodgkin's stage IA is: *(PGI Dec 05)*
A. Chemotherapy is best
B. Radiotherapy is best
C. Total radiation therapy is best treatment
D. Fever and wt loss is always present

226. Treatment of choice in Hodgkin's Lymphoma is:
A. CHOP *(PGI Dec 06)*
B. MOPP
C. ABVD
D. MOPP and ABVD hybrid

227. All of the following statements about Treatment of Hodgkin's lymphoma are true, Except: *(PGI June 07)*
A. ABVD is the most commonly used Regimen
B. Sterility is more frequent after ABVD than MOPP
C. Combination chemotherapy is the mainstay of treatment in Advanced Hodgkin's disease
D. WBC count > 15000/$mm^3$ is a poor prognostic factor

## Non Hodgkins Lymphoma and Leukemia

228. The classification proposed by the International Lymphoma Study Group for non-Hodgkin's lymphoma is known as: *(AI 2005)*
A. Kiel classification.

B. REAL classification.
C. WHO classification.
D. Rappaport classification.

229. Which of the following is not a B-cell neoplasm?
A. Hairy cell leukemia *(AIIMS May 06)*
B. Angiocentric lymphoma
C. Mantle cell lymphoma
D. Burkitt's lymphoma

230. Plasmacytoid Lymphomas may be associated with:
A. IgG *(AI 2010)*
B. IgM
C. IgA
D. IgE

231. "International prognostic index" for lymphoma includes the following prognostic factors except:
A. Stage of disease *(AI 2009)*
B. Number of extralymphatic sites involved
C. LDH
D. Hemoglobin and Albumin

232. 'Intermediate form' of Non hodgkin's lymphoma is :
A. Small non cleaved cell *(AI 1999)*
B. Diffuse, small cleaved cell
C. Lymphoblastic
D. Large cell immunoblastic

233. Intermediate grade of NHL are all *except* : *(NBE)*
A. Diffuse small cell cleaved
B. Diffuse large cell I
C. Mycosis fungoides
D. Diffuse mixed

234. Most malignant form of NHL is : *(NBE)*
A. Diffuse large cell
B. Small cell lymphocytic lymphoma
C. Follicular cleavage
D. Large cell follicular

235. Most common variant of Non-Hodgkin's Lymphoma (NHL) in India is; *(AIIMS Nov 2013)*
A. Diffuse large B-cell lymphoma
B. Follicular Lymphoma
C. Mantle Cell Lymphoma
D. T-cell lymphoblastic lymphoma

236. Most common variant of Lymphoma seen in HIV Patients is: *(NBE)*
A. Immunoblastic Lymphoma
B. Burkitt's Lymphoma
C. Primary CNS Lymphoma
D. Mantle Cell Lymphoma

237. Variant of Immunoblastic Lymphoma primarily seen in HIV Patients is *(NBE)*
A. Primary Effusion Lymphoma
B. Centroblastic Lymphoma
C. Anaplastic Lymphoma
D. Any of the Above

## Burkitt's Lymphoma

238. In Burkitts lymphoma, translocation seen is chromosome *(AIIMS May 01)*
A. 12 - 14 translocation
B. 8 - 14 translocation
C. 4 - 8 translocation
D. 12 - 18 translocation

239. Translocation t(2:8)(p12:q24) is associated with:
A. Chronic Myeloid Leukemia (CML) *(AI 2010)*
B. Acute Myeloid Leukemia (AML)
C. T cell – ALL
D. Burkitt's Lymphoma

240. Burkitt's Lymphoma is associated with which of the following viruses *(NBE)*
A. EBV
B. HTLV-1
C. HHV- 8
D. Adenovirus

241. Burkitt's Lymphoma is associated with: *(AI 2010)*
A. t (8:14)
B. t (11:14)
C. t (15:17)
D. t (14:18)

242. All of the following statements about Burkitt's lymphoma are true, Except: *(PGI June 02)*
A. B cell lymphoma
B. 8, 14 translocation
C. Can present as an abdominal mass
D. Radiotherapy is the treatment of choice

## Hairy Cell Leukemia

243. All of the following statements about Hairy cell leukaemia are true except: *(AI 2004)*
A. Splenomegaly is conspicuous
B. Results from an expansion of neoplastic T lymphocytes
C. Cells are positive for Tartrate Resistant Acid phosphatase
D. The cells express CD25 consistently

244. 'Hairy cell leukemia' is a Neoplastic proliferation of :
A. T. cells *(AI 1999)*
B. B. cells
C. Myeloid cells
D. Macrophages

245. CD 19 positive, CD22 positive, CD103 positive monoclonal B-cells with bright kappa positivity were found to comprise 60% of the peripheral blood lymphoid cells on flow cytometric analysis in a 55 year old man with massive splenomegaly and a total leucocyte count of 3.3 x $10^9$/L. Which one of the following is the most likely diagnosis?
A. Splenic lymphoma with villous lymphocytes
B. Mantle cell lymphoma *(AIIMS Nov. 2004)*
C. B-cell prolymphocytic leukemia
D. Hairy cell leukemia

246. 'Which of the following is NOT used in treatment of hairy cell leukemia: *(AIIMS Feb 97)*
   A. Steroid
   B. Pentostatin
   C. Splenectomy
   D. Alpha-interferon

247. Treatment of choice in hairy cell leukemia is:
   A. Steroid *(NBE)*
   B. Cladribine
   C. Splenectomy
   D. Pentostatin

## Mantle Cell Lymphoma

248. A 63 year old man presents with splenomgaly and lymphadenopathy. Immunophenotype was positive for CD19, CD79b and FMC7. The most likely diagnosis is: *(AIIMS May 01)*
   A. Hairy cell leukemia
   B. Mantle cell Lymphoma (MCL)
   C. Chronic Lymphocytic Leukemia (CLL)
   D. Follicular Lymphoma

249. A 63-year old man presented with massive splenomegaly, lymphadenopathy and a total leucocyte count of 17000 per $mm^3$. The flow cytometery showed CD 19 positive, CD 5 positive, CD 23 negative, monoclonal B-cells with bright kappa positively comprising 80% of the peripheral blood lymphoid cells. The most likely diagnosis is:
   A. Mantle cell lymphoma *(AI 2003)*
   B. Splenic lymphoma with villous lymphocytes
   C. Follicular lymphoma
   D. Hairy cell leukemia

## Chronic Lymphocytic Leukemia (CLL)

250. Chronic Lymphocytic Leukemia (CLL) is associated with:
   A. Individuals > 50 years of age
   B. Mature small lymphocytes in peripheral smear
   C. Hepatosplenomegaly and lymphadenopathy
   D. All of the above

251. 80 year old, asymptomatic man present with a Total Leucocyte Count of 1 lakh, with 80% lymphocytes and 20% PMC's. What is the most probable diagnosis? *(AI 2005)*
   A. HIV
   B. CML
   C. CLL
   D. TB

252. All of the following are true about Chronic Lymphocytic Leukemia, Except: *(PGI 2008)*
   A. Diagnosed on routine blood tests
   B. Leukocytosis is prominent
   C. Can present as acute leukemia
   D. T lymphocyte CLL is more common

253. 80 year old, asymptomatic man present with a Total Leucocyte Count of 1 lakh, with 80% lymphocytes and 20% PMC's. What is the most probable diagnosis? *(AI 2007)*
   A. HIV
   B. CML
   C. CLL
   D. TB

254. A 48 years of woman was admitted with a history of weakness for two months. On examination cervical lymph nodes were found enlarged and spleen was palpable 2 cm below the costal margin. Her hemoglobin was 10.5g/dl. Platelet count $237\times10^9$/L, and total leukocyte count $40\times10^9$/L, which include 80% mature lymphoid cell with coarse clumped chromatin. Bone marrow revealed a nodular lymphoid infiltrate. The peripheral blood lymphoid cells were positive for CD19, CD5, CD20 and were negative for CD79B and FMC(-7). Which one of the following statements is not true about this disease?
   A. Trisomy 12 correlates an aggressive clinical course
   B. Abnormalities of 13q 14 are associated with long term survival *(AIIMS Nov 2004)*
   C. Case with 11q22-23 deletions have excessive lymphadenopathy
   D. t(11;14) translocation is present in most of the cases

255. A 48 year old women was admitted with a history of weakness for two months. On examination, cervical lymph nodes were found enlarged and spleen was palpable 2 cm below the costal margin. Her hemoglobin was 10.5 g/dl, platelet count 2.7×109/L and total leukocyte count $40\times10^9$/L, which included 80% mature lymphoid cells with coarse clumped chromatin. Bone marrow revealed nodular lymphoid infiltrate. The peripheral blood lymphoid cells were positive for CD 19, CD 5, CD20 and CD23 and were negative for CD79B and FMC-7.
   The histopathological examination of the lymph node in this patient will most likely exhibit effacement of lymph node architecture by *(A.I.2005)*
   A. A pseudofollicular pattern with proliferation centers
   B. A monomorphic lymphoid proliferation with a nodular pattern.
   C. A predominantly follicular pattern
   D. A diffuse proliferation of medium to large lymphoid cells with high mitotic rate.

256. A 48 year old woman was admitted with a history of weakness for two months. On examination, cervical lymph nodes were found enlarged and spleen was palpable 2 cm ptatelet count 237 X 109L and total leukocyte count 40 x coarse clumped chromatin. Bone marrow revelaed a nodular lymphoid infiltrate. The peripheral blood lymphoid were negative for CD 19, CD5, CD 20 and CD 23 and were negative for CD 79 B and FMC - 7. *(AIIMS Nov. 05)*

What is the most likely diagnosis?

A. T- cell rich B - cell lymphoma with leukemic spill over in blood.
B. Chronic lymphocytic leukemia
C. Mantle cell lymphoma
D. A definite diagnosis can not be made in this patient without lymph node biopsy

257. In Ritcher's transformation CLL transforms into: *(NBE)*
A. Large B cell Lymphoma
B. Anaplastic carcinoma
C. Burkitt lymphoma
D. Lymphoproliferative lymphoma

258. All of the following statements about treatment of typical CLL are true, except : *(AIIMS May 2013)*
A. Treatment should be initiated as soon as diagnosis is established
B. Chlorambucil and Fludarabine are the most commonly used agents
C. Fludarabine is preferred in the young and Chlorambucil is preferred in the elderly
D. Young patients are candidates for Bone marrow transplantation

## Chronic Myeloid Leukemia (CML) and CMML

259. All of the following statements about Philadelphia Chromosome in CML are true, except: *(AIIMS Nov 2013)*
A. Reciprocal translocation between long arm of chromosome 9 and long arm of chromosome 22
B. The breakpoint cluster region (BCR) is located on the long arm of chromosome 22
C. The ABL gene is located on chromosome 9
D. The Philadelphia chromosome with the oncogenic BCR-ABL gene is found on chromosome 9

260. Peripheral smear with increased neutrophils, basophils, eosinophils, and platelets is highly suggestive of- *(AIIMS May 06)*
A. Acute myeloid leukemia
B. Acute lymphoblastic leukemia
C. Chronic myelogenous leukemia
D. Myelodysplastic syndrome

261. A 60 year old man presented with fatigue, weight loss and heaviness in left hypochondrium for 6 months. The hemogram showed Hb. 10gm/dL, TLC 5 lakhs/$mm^3$, platelet count 4 lakhs/$mm^3$, DLC; neutrophil 55%, lymphocutes 4%, monocytes 2%, basophils 6%, metamyelocytes 10%, myelocytes 18%, promyelocytes 2% and blast 3%. The most likely cytogenetic abnormality in this case is: *(AIIMS May 03)*
A. t (1; 21)
B. t (9; 22)
C. t (15; 17)
D. Trisomy 21

262. In a patient suffering from chronic myeloid leukemia, Hb falls from 11g% to 4g% in a short span of time, and splenomegaly occurs. The cause could be (select two options)- *(PGI June 02)*
A. Accelerated phase
B. CML in blast crisis
C. Ineffective erythropoesis
D. Myelofibrosis

263. Which one of the following is not a criterion for making a diagnosis of chronic myeloid leukemia in accelerated phase : *(AIIMS Nov 2004)*
A. Blasts 10-19% of WBC's in peripheral blood
B. Basophils 10-19% of WBC'S in peripheral blood
C. Increasing spleen size unresponsive to therapy
D. Persistent thrombocytosis (>1000 x $10^9$/L) unresponsive to therapy

264. Leukocyte alkaline phosphate is increased in all, *except* *(AIIMS May 94)*
A. Polycythemia vera
B. CML
C. Myelofibrosis
D. Myeloid metaplasia

265. Which of these is true regarding CML : *(AIIMS 1999)*
A. Size of splenomegaly indicates prognosis
B. Phagocytic activity of WBC is reduced
C. Sudan black stain is specific for myeloblast
D. Myeloblast, granuloblast and lymphoblast become PH chromosome +ve. –ve following remission

266. All of the following are features of juvenile CML *except:* *(AI 94)*
A. Thrombocytopenia
B. Fetal Hb is increased
C. Philadelphia chromosome is positive
D. Lymphadenopathy

267. Haemoglobin F is raised in: *(AIIMS Dec 97)*
A. Juvenile chronic myeloid leukemia
B. Hereditary spherocytosis
C. Congenital red cell aplasia
D. Myasthenia gravis

268. Which of the following conditions is associated with raised levels of FoetalHaemoglobin (HBF): *(NBE)*
A. Juvenile CML
B. Hereditary Spherocytosis
C. Congenital red cell aplasia
D. Myasthenia Gravis

269. Initial treatment recommended for newly diagnosed patient with CML is: *(NBE)*
A. Allogenic Bone Marrow Transplantation
B. Imatinib Mesylate Therapy
C. TNF-α
D. IFN-α

270. Chemotherapeutic Agent of Choice for the treatment of CML is: *(NBE)*
A. Imatinib
B. Vincristine
C. Cyclophosphamide
D. Methotrexate

271. Drug of choice for chronic myeloid Leukemia (CML) is: *(AI 2008)*
A. Hydroxyurea
B. Imatinib
C. Inflliximab
D. IFN

272. Drug of choice for treatment of CML is: *(NBE)*
A. Imatinib
B. Hydroxyurea
C. IFN-Alfa
D. Infliximab

273. Best Rx for CML is: *(PGI Dec 98)*
A. Autologous BMT
B. Allogenic BMT
C. Alpha Interferon
D. Hydroxyurea

274. Which of the following is not compatible with a diagnosis of chronic myelomonocytic leukemia? *(AIIMS Nov 03)*
A. Peripheral blood monocytosis more than 1×109L
B. Absence of Philadelphia chromosome
C. More than 20% blasts in blood or bone marrow
D. Absent or minimal dysplasia in myeloid lieages.

### Mycosis Fungoides

275. Mycosis fungoides which is not true
A. It is the most common form of cutaneous lymphoma *(AI 2007)*
B. Pautriers microabscess
C. Indolent course and easily amenable to treatment
D. Erythroderma seen and spreads to peripheral circulation

## Acute Leukemia

### General Characteristics

276. The marker for B lymphocyte is- *(NBE)*
A. CD 19
B. CD 68
C. CD 34
D. CD 4

277. Which of the following is a pan-T lymphocyte marker: *(AI 2003)*
A. CD2
B. CD3
C. CD19
D. CD25

278. Marker specific for myeloid lineage- *(AIIMS Nov 95)*
A. CD33
B. CD14
C. CD13
D. MPO

279. Memory T cells can be identified by using the following marker *(AI 2003)*
A. CD45RA
B. CD45RB
C. SD45RC
D. CD45RO

280. Which of the followings combinations of cytogenetic abnormality and associated leukemia/lymphoma is incorrect? *(AIIMS Nov 2004)*
A. t (8:14): Burkitts lymphoma
B. t (15:17) : AML-M3
C. t (9:22) : CML
D. t (9:20) : ALL

### Acute Lymphoid Leukemia (ALL)

281. The most common type of ALL is: *(NBE)*
A. Pre B cell ALL
B. T cell ALL
C. B cell ALL
D. Biphenotypic ALL

282. Which of the following presents as mediastinal enlargement: *(NBE)*
A. Promyelocytic Leukemia
B. CML
C. ALL
D. Diffuse histiocytic lymphoma

283. A17-year-old boy presented with TLC of $138\times10^9$/ L with 80% blasts on the peripheral smear. Chest X-ray demonsnstrated a large mediastinal mass. Immunophenotyping of this patent's blasts would most likely demonstrate: *(AIIMS May 2006)*
A. No surface antigens (null phenotype)
B. An immature T cell phenotype (Tdt/CD34/CD7 positive)
C. Myeloid markers, such as CD13,CD33 and Cd15
D. B cell markers, such as CD19,CD20 and CD22

284. All of the following are good prognostic factors for childhood. ALL except: *(AIIMS May 02, AI 07)*
A. Hyperdiploidy
B. Female sex
C. Pre B cell ALL
D. t (12 : 21) translocation

285. Good prognostic Factors for ALL include all of the following, Except: *((NBE))*
A. Hyperdiploidy
B. Female sex
C. Pre B cell ALL
D. t (12 : 21) translocation

286. Which of the following is a poor prognostic factor for childhood ALL. *(AIIMS Nov 09)*
A. Total Leukocyte count 4000-100,000

B. Age < 2 years
C. Testicular involvement
D. Blasts in peripheral smear

287. Which of the following is a good prognostic factor in ALL: *(PGI 2008)*
A. High WBC count
B. Male sex
C. Age < 2 years
D. Hyperdiploidy

288. Lasparaginase is particularly used in which type of leukemia- *(AI 1996)*
A. AML
B. CML
C. ALL
D. CLL

289. Treatment of choice in intracranial ALL is:
A. A. Intrathecal methotrexate *(PGI June 99)*
B. Vincristine and prednisolone
C. Intrathecal vincristine
D. Prednisolone

290. In which of the following types of leukemia is methotrexate administered for CNS prophylasxis:
A. ALL
B. AML
C. CLL
D. CML

291. All of the following drugs are used in management of ALL Except: *(PGI June 02)*
A. Methotrexate
B. All – trans retinoic acid
C. Prednisolone
D. L-Asparginase
E. Vincristine

292. Which of the following enzymes is used in the treatment of Acute Lymphocytic Leukemia *(NBE)*
A. Asparginase
B. Amylase
C. Lipase
D. Transaminase

293. A four year old boy was admitted with a history of abdominal pain and fever for two months maculo papular rash for ten days, and dry cough, dyspnea and wheezing for three days. One examination liver and spleen were enlarged 4 cm and 3 cm respectively below the costal margins. His hemoglobin was 10.0 g/dl, platelet count 37×109/L and total leukocyte count 70 × 109L, which included 80% eosinophils Bone marrow examination revealed a cellular marrow comprising of 45% blasts and 34% Eosinophils and eosinophilic precursors. The blasts stained negative for myeloperoxidase and non-specific esterase and were positive for CD19, CD10, CD22 and CD20. Which of the following is the most likely diagnosis?
A. Biphenotypic acute leukemia (lymphoid and eosinophil lineage *(AIIMS Nov 2004)*
B. Acute eosinophilic leukemia
C. Acute lymphoblastic leukemia with hypereosinophilic syndrome
D. Acute myeloid leukemia with eosinophilia

294. A four year old boy was admitted with a history of abdominal pain and fever for two months, maculopapular rash for ten days, and dry cough, dyspnea and wheezing for three days. On examination, liver and spleen were enlarged 4 cm and 3 cm respectively below the costal margins. His hemoglobin was 10.0 g/dl, platelet count $37 \times 10^9$/L and total leukocyte count $70 \times 10^9$/L, which included 80% eosinophils. Bone marrow examination revealed a cellular marrow comprising 45% blasts and 34% eosinophils and eosinophilic precursors. The blasts stained negative for myeloperoxidase and non-specific esterase and were positive for CD19, CD10, CD22 and CD20. Which one of the following statements in not true about this disease? *(AI 2005)*
A. Eosinophils are not part of the Neoplastic clone.
B. t(5:14) rearrangement may be detected in blasts.
C. Peripheral blood eosinophilia may normalize with chemotherapy.
D. Inv (16) is often detected in the blasts and the eosinophils.

## Acute Myeloblastic Leukemia (AML)

295. Most common type of acute myeloid leukemia:
A. M2 *(NBE)*
B. M3
C. M4
D. M5

296. Which of the following is a poor prognostic factor in Acute Myeloid Leukemia (AML)
A. Monosomy *(AIIMS Nov 2010)*
B. Deletion of X or Y chromosome
C. t (8; 21) translocation
D. Nucleophosphin mutation

297. Auer Rods are most frequently seen in which subtype of AML *(NBE)*
A. M0
B. M 3
C. M 5
D. M 7

298. Auer Rods are typically not seen in: *(NBE)*
A. AML – M0
B. AML – M2
C. AML – M3
D. AML – M1

299. All of the following are poor prognostic factors for acute myeloid leukemias, *except*: *(AI 2003)*
A. Age more than 60 years
B. Leucocytes count more than 1,00,000/µl
C. Secondary leukemias
D. Presence of t(8:21)

300. A child with Acute myeloid Leukemia presents with Hyperleukocytosis. Treatment includes all of the following, Except: *(NBE)*
A. IV fluids
B. Allopurinol
C. Alkalinization
D. Immediately start induction chemotherapy

301. Poor prognosis in AML is indicated by: *(AI 2008)*
A. Inversion 16
B. Translocation 15/17 (t15; 17)
C. Normal cytogenecity
D. Monosomy 7

302. AML with worst prognosis is :
A. 8/21 translocation *(AIIMS Nov 2006)*
B. Inversion 16
C. Normal Cytogenetics
D. Monosomy 7

303. In PML, all of the following are seen except :
A. Retinoic acid is used in treatment
B. 15/17 translocation *(AI 2007)*
C. CD 15/34 both seen in same cell
D. Associated with DIVC

304. A 15-years-old boy presented with one day history of bleeding gum,subconjunctival bleed and purpuric rash. Investigations revealed followed results:Hb- 6.4 gm/dl; TLC-26, 500/mm3 platelet 35,000 mm3; prothrombin time-20 sec with a control of 13 sec; partial thromboplastin time-50sec; and Fibrinogen 10mg/dL.Peripheral smear was suggestive of acute myeloblastic leukemia. Which of the following is the most likely? *(AIIMS May 2006)*
A. Myeloblastic leukemia without maturation
B. Myeloblastic leukemia with maturation
C. Promyelocytic leukemia
D. Myelomonocytic leukemia

305. Arsenic is used in treatment of: *(AIIMS May 07)*
A. Acute promyelocytic leukemia
B. A.L.L
C. CML
D. Transient myeloproliferative disorder

**Biphenotypic Leukemia**

306. In a patient with acute leukemia, immunophenotype pattern is CD 19+ve, CD 10+ve, CD33+ve, CD13+ve. He may probably have- *(AIIMS May 04)*
A. Biphenotypic leukemia
B. ALL
C. AML-M2
D. AML-Mo

## Plasma Cell Disorders / Multiple Myeloma

307. All the following are seen in Multiple myeloma *except* *(NBE)*
A. Visual Disturbance
B. Bleeding tendency
C. Proteinuria
D. Dystrophic calcification

308. All of the following are seen in multiple myeloma except: *(NBE)*
A. Visual Disturbance
B. Proteinuria
C. Bleeding tendency
D. Dystrophic calcification

309. Which of the following is the least common feature of Multiple Myeloma: *(AI 2012)*
A. Bone pain
B. Normocytic Normochromic Anemia
C. Susceptibility to bacterial infection
D. Hyperviscosity syndrome

310. Which of the following is not a major criteria for diagnosis of multiple myeloma? *(AI 2006)*
A. Lytic bone lesions
B. Plasmacytoma on tissue biopsy
C. Bone marrow plasmacytosis > 30%
D. 'M' spike > 3g% for Ig G, > 2g% for IgA

311. Which is not a minor criteria of Multiple Myeloma?
A. Multiple lytic lesions *(AIIMS Nov 2008)*
B. Plasmacytosis > 20%
C. Plasmacytoma in tissue
D. S. IgG > 3gm, IgA > 1.5

312. All of the following are minor criteria for multiple Myeloma, Except *(AIIMS Nov 2010)*
A. Plasmacytosis 20%
B. Multiple lytic lesions
C. Plasmacytoma on tissue biopsy
D. Monoclonal Ig spike < 2g/dl for IgA and < 3.5 for IgG

313. All seen in multiple myeloma, *except* :
A. Lytic bone lesion *(AIIMS May 95*
B. Hypercalcemia
C. Plasmacytosis of bone marrow > 2%
D. Decreased serum alkaline phosphatase activity

314. The immunoglobulin least commonly involved in Multiple Myeloma is : *(NBE)*
A. IgG
B. IgM
C. IgA
D. IgD

315. The immunoglobulin least commonly involved in Multiple Myeloma is: *(NBE)*
A. IgG
B. IgM
C. IgA
D. IgD

316. The most common translocation seen in patients with Multiple Myeloma is *(NBE)*
A. t(11;14)
B. t(4;14)
C. t(14;16)
D. t(14;20)

317. The most common translocation associated with poor prognosis in patients with Multiple Myeloma is
A. t(11;14) *(NBE)*

B. t(4;14)
C. t(14;16)
D. t(14;20)

318. All the following are true about multiple myeloma *except:* *(AI 1994)*
A. Osteolytic bone disease
B. t(8-14) translocation
C. Light chain proliferation
D. Bence-Jones proteins in urine

319. All of the following are true about multiple myeloma except- *(NBE)*
A. Osteolytic bone disease
B. t (8-14) translocation
C. Light chain proliferation
D. Bence-jones proteins in urine

320. True about Myeloma is all, *except* *(AIIMS Nov 01)*
A. Plasma cell clonal proliferation
B. Common after 50 yrs of age
C. Amyloidosis can occur
D. Protein casts in urine are made up of complete Ig chains

321. Commonest site of lytic lesion, in multiple myeloma is
A. Vertebral column *(AIIMS Dec 97)*
B. Femur
C. Clavicle
D. Pelvis

322. Which of the following may be seen in Multiple Myeloma: *(PGI June 05)*
A. Decreased Calcium
B. Sclerotic bone lesion
C. Bone deposition
D. Renal failure

323. The following is the least useful investigation in multiple myeloma : *(AI 2007)*
A. ESR
B. X-Ray
C. Bone scan
D. Bone marrow biopsy

324. An elderly male presents with headache, recurrent infections and multiple punched out lytic lesions of x-ray skull. The investigation that will best help in establishing a diagnosis is: *(AI 2009)*
A. Protein Electrophoresis
B. Serum calcium
C. Alkaline phosphatase levels
D. Acid phosphatase levels

325. Which is not seen in multiple myeloma :
A. Anemia *(AIIMS Feb 97)*
B. Increased alkaline phosphatase
C. Hypercalcemia
D. $\uparrow^{ed}$ ESR

326. True regarding multiple myeloma is all. *except* :
A. Bone pain *(AI 1998)*
B. Lytic lesions
C. Increased alkaline phosphatase
D. Tarterate resistance acid phosphatase positive

327. Raised serum alkaline phosphatase is seen in all, *except* *(AIIMS Dec 94)*
A. Paget's disease
B. Multiple myeloma
C. Osteomalacia
D. Hyperthyroidism

328. Which one of the following is not a feature of multiple myeloma? *(NBE)*
A. Hypercalcemia
B. Anemia
C. Hyperviscosity
D. Elevated alkaline phosphatase

329. Maximum ESR is seen in : *(AI 1998)*
A. CHF
B. Polycythemia vera
C. Multiple myeloma
D. Sickle cell anemia

330. In multiple myeloma following are seen except:
A. Anion gap raised *(PGI Dec 97)*
B. Lytic bone lesion
C. Polyarticular pain
D. M spike present with polyarticulopathy

331. Multiple myeloma is characterized by all except:
A. Presence of light chains *(PGI 2000)*
B. Monoclonal gammopathy
C. Polyclonal gammopathy
D. Hypergammaglobulinemia

332. True about Multiple myeloma are all Except:
A. Bence Jones protein in urine *(PGI 2000)*
B. Hypogammaglobulinemia
C. Amyloidosis
D. Plasmacytosis < 10%
E. Renal failure

333. Russell bodies are found in- *(AI 96)*
A. Multiple Myeloma
B. Gonadal tumor
C. Parkinsonism
D. Intracranial neoplasms

334. Russell body is found in- *(AIIMS June 97, AI 95)*
A. WBC
B. RBC
C. Mast cells
D. Plasma cells

335. 'Rain drop'skull is seen in: *(NBE)*
A. Burkitt's lymphoma
B. Hodgkin's lymphoma
C. Multiple myeloma
D. Haemophilia

336. All of the following are poor prognostic factors in Multiple Myeloma, Except: *(PGI June 99)*
A. Azotemia
B. Hypocalcemia
C. ↑ LDH
D. Chromosoma 13 deletion
E. High M component production

337. A patient of multiple myeloma presents with bony lesions. What is the best marker for prognosis of the disease: *(AIIMS June 99; AIIMS 2000)*
   A. Bone marrow plasma cell
   B. Serum calcium level
   C. Beta 2 microglobulin
   D. Beta 1 microglobulin

338. A 58 years old woman, who had backache and recurrent chest infections for 6 months, develops sudden weakness of the legs and urinary retention. Her investigations show hemoglobin of 7.3 gm/dl, serum calcium 12.6 mg/dl, phosphate 2.5 mg/dl, alkaline phosphatse 100 u/l, serum albumin 3 gm/dl, globulin 7.1 gm/dl, and urea 178 mg/dl. What is the most likely diagnosis ? *(AI 06)*
   A. Lung cancer
   B. Disseminated tuberculosis
   C. Multiple myeloma
   D. Osteoporosis

339. Ramla, 65 yrs old male, presents with low back pain especially at L3, anaemia and fatigability. His investigation profile reveals – Hb = 7 gm%, TLC-9000/cmm, DLC -N- 55%, L-30%, M-10%, E-1%, B-2%, Serum proteins-8 gm %, ratio-2.9/5.9, ESR-90 and serum creatinine-3.2 mg%. Likely diagnosis is :
   A. Waldenstroms macroglobulinemia
   B. Multiple myeloma *(AIIMS Nov 01)*
   C. TB spine
   D. Secondaries in spine

340. Which of the following drugs is not used for the management of multiple myeloma *(NBE)*
   A. Bortezomib
   B. Hydroxyurea
   C. Melphelan
   D. Cyclophosphamide

341. All of the following drugs are used in the treatment of Multiple myeloma, Except: *(PGI 09)*
   A. Bortezomib
   B. Melphelan
   C. Hydroxyurea
   D. Cyclophosphamide

**Multiple Myeloma Variance and Other Plasma Cell Disorders**

342. True about smoldering myeloma is: *(PGI June 2008)*
   A. Monoclonal gammopathy
   B. Lytic bone lesion
   C. Hypercalcemia
   D. Bone Marrow Plasma cell < 10%

343. An 80 year old asymptomatic woman was detected to have a monoclonal spike on serum electrophoresis (IgG levels 1.5 g/dl). Bone marrow revealed plasma cells of 8%. The most likely diagnosis is: *(AI 2004)*
   A. Multiple myeloma
   B. Indolent myeloma
   C. Monoclonal gammopathy of unknown significance
   D. Waldenstorm's macroglobulinemia

344. Ramesh 60 years, presents with generalized bone pain. On examination there is elevated ESR of 100 mm, serum globulin 7, lytic lesions in the skull, serum creatinine of 3.5 mg/dL and serum calcium of 11 mg/dL. What is the most likely diagnosis :
   A. Waldenstrom's macroglobulinemia
   B. Multiple myeloma *(AIIMS Nov. 2000)*
   C. Hyperparathyroidism
   D. Osteomalacia

345. Which of the following statement is not true?
   A. Patients with IgD myeloma may present with no evident M-spike on serum electrophoresis.
   B. A diagnosis of plasma cell leukemia can be made if circulating peripheral blood plasmablasts comprise 14% of peripheral blood white cells in a patient with white blood cell count of $1 \times 10^9$/L and platelet count of $88 \times 10^9$/L. *(AI 2005)*
   C. In smoldering myeloma plasma cells constitute 10-30% of total bone marrow cellularity.
   D. In a patient with multiple myeloma, a monoclonal light chain may be detected in both serum and urine

346. A Patient presents with renal failure and bone pain. X-rays show evidence of skeletal destruction. Laboratory evaluation reveals hypercalcemia. Serum Electrophoresis shows a prominent M spike. Tissue biopsy shows Plasmacytoma. Bone marrow shows plasmacytosis with 35 percent Plasma cells. The most likely diagnosis is: *(AIIMS May 2013)*
   A. Multiple Myeloma
   B. Plasmacytoma
   C. MGUS
   D. Smoldering Myeloma

347. A patient presents with evidence of lytic lesion in the bone. Histology from the bone lesion reveals monoclonal plasma cells. Bone marrow biopsy from the from the sternum shows <10 percent Plasma cells. Skeletal Survey is otherwise unremarkable. A small positive M spike is reported on electrophoresis. The diagnosis is: *(AIIMS MAY 2013)*
   A. Multiple Myeloma
   B. Plasmacytoma
   C. Smoldering Myeloma
   D. Lymphoma

348. Most common heavy chain disease is:
   A. Franklin disease *(NBE)*
   B. Seligmann disease
   C. Mu heavy chain dise4ase
   D. Waldenstron cryoglobulinemia

349. Franklin's disease is associated with: *(AIIMS May 95)*
   A. Gamma heavy chain disease
   B. Multiple myeloma
   C. Alpha heavy chain disease
   D. Waldenstorm's macroglobulinemia

350. Heavy chain disease with Kappa light chains in urine: *(NBE)*
A. Mu chain disease
B. Seligman disease
C. Franklin disease
D. Waldenstrom macroglobulinemia

## Bleeding / Coagulation Disorder

### General

351. Vitamin K dependent coagulation factors include: *(AI 2010)*
A. II and III
B. IX and X
C. III and V
D. VIII and XII

352. Vitamin K-dependent factor is-
A. II
B. III
C. IV
D. VI

353. Which is most likely to be increased in Vit K deficiency: *(AI 2000)*
A. P.T.T.
B. P.T.
C. Platelet count
D. Fibrinogen time

354. Feature of hemorrhagic disease of new born is- *(AIIMS June 97)*
A. Prolonged prothrombin time
B. Defective platelet count
C. Prolonged bleeding time
D. Prolonged thrombin time

355. A 78 year old man who lives alone and prepares his own food is found to have ecchymotic patches over posterior aspect of his lower extremities. He has haemorrhagic areas around hair follicles, hair are fragmented and splinter haemorrhages are present in nail beds and several hematomas are present in the muscles of arms and legs. PT and CT are normal. This clinical syndrome is most likely due to : *(AIIMS Nov 99)*
A. Vitamin K deficiency
B. Vitamin C deficiency
C. Pyridoxine deficiency
D. Vitamin A deficiency

356. A patient is on aspirin, what will be the finding? *(AI 2007)*
A. Prolonged BT
B. Prolonged PT
C. Prolonged APTT
D. Prolonged CT

357. Platelet function may be assessed by (select two options): *(PGI Dec 02)*
A. Platelet adhesion Assays
B. BT
C. CT
D. PTT
E. APTT

358. Which of the following is not involved in intrinsic pathway? *(AI 2009)*
A. Factor XII
B. Factor XI
C. Factor IX
D. Factor VII

359. Which of the following helps in bridging the fibrin in a clot and stabilizes the clot? *(AI 2009)*
A. Factor XIII
B. Factor V
C. Factor VIII
D. Factor III

360. Converging point of both pathway in coagulation is at: *(PGI June 99)*
A. Factor VIII
B. Stuart factor X
C. Factor IX
D. Factor VII

361. Which of the following may present with isolated prolongation of prothrombin time (PT): *(NBE)*
A. Factor VIII deficiency
B. Factor VII deficiency
C. Factor XII deficiency
D. Factor IX deficiency

362. A patient has normal PT and Platelet Count. The aPTT is increased and factor VIII levels are observed to be 60 Iu/dL (60%). There is no associated history of bleeding even after a surgical procedure. The most likely diagnosis is: *(AIIMS Nov 2011)*
A. Factor IX deficiency
B. Factor VIII inhibitors
C. Lupus anticoagulant
D. Thalassemia

363. Both PT and APTT are prolonged in *(NBE)*
A. Factor II Deficiency
B. Thrombocytopenia
C. Factor VII Deficiency
D. Heparin Therapy

364. A child underwent a tonsillectomy at 6 years of age with no complications. He underwent a preoperative screening for bleeding at the age of 12 years before an elective laparotomy, and was found to have a prolonged partial thromboplastin time but normal Prothrombin time. There was no family history of bleeding. The patient is likely to have- *(AIIMS Nov 2004)*
A. Acquired vitamin K deficiency
B. Acquired liver disease
C. Factor XII deficiency
D. Mild hemophilia A

365. A 35 year old lady presents with an isolated prolongation of aPTT. Prothrombin time (PT) and platelet count are normal and there is no obvious bleeding tendency. Two years back, she was operated for cholecystectomy and had no adverse bleeding episode. Which of the following should be the next step in evaluating this patient

A. Factor VIII Assay *(AIIMS Nov 2010)*
B. Platelet aggregation test
C. Russell viper venom assay
D. Ristocetin cofactor assay

366. Which of the following statements about coagulation factor VII is not true *(AI 2009)*
A. Deficiency is inherited as an Autosomal Recessive trait
B. Deficiency is associated with prolonged APTT
C. Deficiency can be managed by Fresh Frozen plasma
D. Has a shorter half life in comparison to Hageman factor (XII)

367. Most common inherited bleeding disorder:
A. Von wilebrand disease *(NBE)*
B. Bernard soulier
C. Glanzmann thrombasthenia
D. ITP acute

368. Spontaneous muscle bleeding is typically seen in:
A. Hemophilia *(NBE)*
B. Afibrinogenemia
C. Von Willebrand's disease
D. Scott's syndrome

## Hemophilia

369. True about Haemophilia A are all *except* :
A. PTT increased *(AI 2001)*
B. PT increased
C. Clotting time is increased.
D. Serum levels of factor VIII are decreased.

370. Hemophilic A has following diagnostic features except- *(AI 97)*
a) ↓ VIII factor
b) ↑ PTT
c) ↑ PT
d) Normal BT

371. All are true about hemophilia, *except*
A. Increased Bleeding time (BT)
B. Decreased factor VIII *(AIIMS May 94)*
C. Decreased factor IX
D. Increased partial thromboplastin time (PTT)

372. Which of the following feature may be used to differentiate hemophilia A from von Willebrand disease. *(NBE)*
A. Bleeding time
B. Prothrombin time
C. Partial thromboplastin time
D. Factor VIII levels

373. Recurrent Spontaneous Hemarthrosis is commonly seen in patients with Hemophilia when factor VIII levels are: *(NBE)*
A. < 36 %
B. <10%
C. <5%
D. <1 %

374. The most common manifestation of moderate /severe Hemophilia A is: *(NBE)*
A. Recurrent Hemarthrosis
B. Recurrent muscle bleeding
C. Recurrent bleeding from gums
D. Recurrent Hematuria

375. The most common cause of fracture in a patient with Hemophilia is *(NBE)*
A. Osteoporosis and Restricted Joint Movement
B. Osteonecrosis
C. Iron deposition
D. Pseudo-tumors

376. In a patient of Hemophilia to be taken for dental extraction true is all, *except* *(AIIMS Nov 01)*
A. All patients should be screened for HIV
B. Extraction should be done under general anaesthesia and skilled anaesthetic care
C. Factor VIII or cryoprecipitate can be needed
D. Dose of Lignocaine required for anaesthesia is same as that for normal individuals

## Von Willebrands Factor (VWF) Disease

377. The coagulation profile in a 13-year old girl with Menorrhagia having Von Willebrands disease is:
A. Isolated prolonged PTT with a normal PT
B. Isolated prolonged PT with a normal PTT
C. Prolongation of both PT and PTT *(NBE)*
D. Prolongation of thrombin time

378. Von Willebrand Disease is associated with : *(NBE)*
A. ↑PTT ; ↓PT; ↑BT; ↑CT
B. ↑PTT ; ↑PT; ↑BT; ↑CT
C. ↑PTT ; Normal PT; ↑BT; Normal CT
D. ↑PTT ; Normal PT; ↑BT; ↑CT

379. True about Von Willebrand's disease is all *except* :
A. Increased bleeding time *(AIIMS 2000)*
B. Factor VIII c levels are decreased in circulation.
C. Increased platelet aggregation in response to Ristocetin
D. APTT is increased

380. True about Von Willebrand's disease is all *except* :
A. Increased bleeding time *(AIIMS 2000)*
B. Factor VIII c levels are decreased in circulation.
C. Defect in VWF is detected by ristocetin
D. APTT is increased

381. A seven year old girl presents with repeated episodes of bleeding into joints. APTT is prolonged and PT is normal. The most likely diagnosis is. *(AI 2009)*
A. Factor VIII deficiency (Hemophilia A)
B. Factor VII deficiency
C. Von Willebrand Disease
D. Factor XII deficiency

382. Best assay for deficiency of von Willebarnd factor is:
A. Bleeding time *(PGI Dec 01)*
B. BT + APTT

C. BT + APTT + vWF-ristocetin factor assay
D. PT

383. The commonest mode of inheritance of Von Willebrand's disease : *(AIIMS Dec 97)*
A. Codominant
B. Autosomal recessive
C. Autosomal dominant
D. X-linked recessive

## Platelet Function Disorders

384. All of the following are inherited platelet function disorders Except: *(NBE)*
A. Bernard Soulier syndrome
B. Glanzman Thrombasthenia
C. Wiskott Aldrich Syndrome
D. Von-Willebrand disease
E. Weber-Christian disease

385. Wiskott Aldrich syndrome is characterized by all Except: *(AIIMS Nov 2009)*
A. Thrombocytopenia
B. Autosomal recessive
C. Failure of aggregation of platelets in response to agonists
D. Eczema

386. A patient presents with Thrombocytopenia, eczema and recurrent infection. The most probable diagnosis is: *(NBE)*
A. Wiskott Aldrich syndrome
B. Chediak-Higashi syndrome
C. Job's syndrome
D. Bruton's Agammaglobulinemia

**387.** All of the following statements about Wiskott-Aldrich syndrome are true, Except*(AIIMS NOV 2008)*
A. Autosomal Recessive disorder
B. Eczematous Rash
C. Impaired platelet aggregation in response to agonist
D. Thrombocytopenia

388. The presence of small sized platelets on the peripheral smear is characteristic of: *(AIIMS Nov. 03)*
A. Idiopathic thrombocytopenic purpura
B. Bernard soulier syndrome
C. Disseminated intravascular coagulation
D. Wiskott Aldrich syndrome

389. Which is not true regarding Bernard soulier syndrome?
A. Ristocetin aggregation is normal *(AI 2007)*
B. Aggregation with collagen and ADP is normal
C. Large platelets
D. Thrombocytopenia

## Thrombocytopenia and Purpura

390. Thrombocytopenia is not seen in: *(AI 1996)*
A. H.S. purpura
B. DIC
C. Leukemia
D. Metastasis

391. All of the following can cause megakaryocytic thrombocytopenia, except- *(AIIMS Nov 04)*
A. Idiopathic thrombocytopenic purpura
B. Systemic lupus erythematosus
C. Aplastic anemia
D. Disseminated intravascular coagulation (DIC)

392. Thrombocytopenia occurs in all *except*: *(AI 2001)*
A. Henoch schonlein purpura
B. TTP
C. DIC
D. Wiskott Aldrich syndrome

393. Platelet count is decreased in all of the following condition *except*: *(AIIMS Dec 98)*
A. H. S. Purpura
B. Idiopathic thrombocytopenic purpura
C. Thrombotic thrombocytopenic purpura
D. Systemic lupus erythematosus

394. Auto immune destruction of platelets is seen in
A. SLE
B. Chronic Lymphocytic leukemia
C. HIV
D. All the above

395. Autoimmune destruction of platelet is seen in :
A. SLE *(AIIMS May 95)*
B. Rheumatoid arthritis
C. Reiter disease
D. Polyarteritis nodosa

396. Palpable purpura could occur in the following conditions, *except*: *(AI 2005)*
A. Thrombocytopenia.
B. Small-vessel vasculitis.
C. Disseminated gonococcal infection.
D. Acute meningococcemia.

397. Palpable purpura is seen in *(AIIMS May 94)*
A. Idiopathic thrombocytopenic purpura (ITP)
B. Scurvy
C. Henoch Sconlein Purpura
D. Monoclonal cryoglobulinemia

## Idiopathic Thrombocytopenic Purpura (ITP)

398. Cause of ITP is : *(AIIMS Feb 97)*
A. Vasculitis
B. Antibody to vascular epithelium
C. Antibody to platelets
D. Antibody to clotting factors

399. Idiopathic thrombocytopenic purpura is associated with all of the following Except:
A. Splenomegaly
B. Mucosal bleeding
C. Thrombocytopenia
D. Increased megakaryocytes

400. Which of the following statements about Acute Immune Thrombocytopenic Purpura is not true:
A. Autoimmune Mediated *(PGI 09)*

B. Massive Splenomegaly
C. Increased Megakaryocytes in marrow
D. IV immunoglobulins may be required
E. Usually self limiting condition

401. A six year old boy presents with echymoses and petichiae all over the body 2 weeks after an upper respiratory tract infection Abdominal examination is unremarkable with no hepatosplenomegaly All of the following statements about the affecting condition are true Except: *(AIIMS Nov 99)*
A. Bleeding into the joints is a common manifestation
B. Bone marrow will show increased megakaryocytes
C. Platelet count is decreased
D. Condition resolves spontaneously in 80% of patients in 2 to 6 weeks

402. All of the following features about Idiopathic Thrombocytopenia are true, Except:
A. Acute ITP is often proceded by Viral infections
B. Chronic ITP is common in females
C. Spontaneous remission is common in Chronic ITP
D. Acute ITP is more common in children

403. The following laboratory determinants is abnormally prolonged in ITP : *(AI 2002)*
A. APTT
B. Prothrombin time
C. Bleeding time
D. Clotting time

404. Platelet transfusion is not indicated in: *(AI 1996)*
A. Dilutional Thrombocytopenia
B. Immunogenic Thrombocytopenia
C. Aplastic Anemia
D. DIC

## Thrombotic Thrombocytopenic Purpura (TTP)

405. All of the following feature may be seen in thrombotic thrombocytopenic purpura, *except* :
A. Fever *(AI 2002)*
B. Haemolysis
C. Hypertension
D. Low platelets count

406. All of the following statements about Thrombotic thrombocytopenic purpura (TTP) are true, Except :
A. Microangiopathic Hemolytic Anemia
B. Thrombocytopenia
C. Normal complement levels
D. Grossly abnormal coagulation tests

407. Thrombotic thrombocytopenic purpura is a syndrome characterized by: *(NBE)*
A. Thrombocytosis, anemia, neurologic abnormalities, progressive renal failure and fever.
B. Thrombocytopenia, anemia, neurologic abnormalities, progressive hepatic failure and fever
C. Thrombocytosis, anemia neurologic abnormalities, progressive renal failure and fever
D. Thrombocytopenia, anemia, neurological abnormalities, progressive renal failure and fever

408. All of the following are features of Thrombotic Thrombocytopenic purpura, Except *(AIIMS June 90)*
A. Fever
B. Hemolysis
C. Hypertension
D. Low platelet count

409. A person presents with fever and altered consciousness. Investigations reveal anemia with fragmented red blood cells, platelet count of $20,000/mm^3$, serum creatinine of 3.0 mg % and normal PT and aPTT.
Which of the following is the most appropriate treatment for the patient: *(PGI 09)*
A. Plasma Exchange Therapy
B. Corticosteroids and Intravenous Immunoglobulins
D. Anticoagulation with Heparin
E. Platelet transfusion

410. All of the following are used in the treatment of Thrombotic Thrombocytopenic Purpura, Except. *(PGI -09)*
A. Plasmapharesis
B. Corticosteroids
C. Immunotherapy
D. Heparin
E. Platelet transfusion

## Disseminated Intravascular Coagulation (DIC)

411. Causes of DIC include: *(PGI Dec 04)*
A. Leukemia
B. Masive transfusion
C. Abruptio placentae
D. All of the above

412. Causes of DIC include: *(PGI Dec 05)*
A. Lymphoma
B. Leukemia
C. Adenocarcinoma Prostate
D. Snake venom
E. All of the above

413. False statement regarding DIC is: *(AI 2001)*
A. Thrombocytopenia
B. Decreased fibrinogen
C. Decreased PTT
D. Increased PT

414. The following is the finding seen in DIVC :
A. Increased fibrinogen , increased antithrombin III, increased thrombin-antithrombin III complexes
B. Increased FDP, decreased PT, increased antithrombin III *(AI 2007)*
C. Increased FDP, prolonged PT, increased thrombin-antithrombin complexes
D. Increased FDP, prolonged PT, reduced Platlets

415. The most sensitive test for DIC is: *(AI 2001)*
A. Serum fibrinogen levels
B. Serum levels of fibrin degradation products (FDP)
C. Prolonged PT and PTT
D. Thrombocytopenia

416. Which of the following features is NOT seen in DIC?
A. Thrombosis *(NBE)*
B. Thrombocytopenia
C. Hyperfibrinogenemia
D. Consumption coagulopathy

417. Bleeding in DIC is most closely related to:
A. Raised fibrin degradation products level in blodd
B. Prolong prothrombin time *(AIIMS June 98)*
C. Low serum fibrinogen level
D. Raised thrombin time

418. DIC is commonly seen in- *(NBE)*
A. MI AML
B. M2 AML
C. M3 AML
D. M4 AML

419. Disseminated intravascular coagulation (DIC) differs from thrombotic thrombocytopenic purpura. In this reference the DIC is most likely characterized by:
A. Significant numbers of schistocytes
B. A brisk reticulocytosis *(AI 2004)*
C. Decreased coagulation factor levels
D. Significant thrombocytopenia

## Hypercoagulable States / Thrombosis

### General

420. All are hypercoagulable states, except :
A. Protein C resistance *(AIIMS June 98)*
B. Factor V Leiden deficiency
C. Antiphospholipid antibody
D. Polycythemia

421. All of the following conditions are associated with venous and arterial thrombotic events, except: *(AIIMS May 2011)*
A. Paroxysmal Nocturnal Haemoglobinuria (PNH)
B. Disseminated Intravascular Coagulation
C. Idiopathic Thrombocytopenic Purpura (ITP)
D. Heparin Induced Thrombocytopenia (HIT)

422. All of the following conditions predispose to thrombosis *except*: *(AIIMS Dec 98)*
A. Paroxysmal nocturnal hemoglobinuria
B. Homocystinurea
C. Hypomagnesemia
D. Behcets syndrome

423. Coagulation defects associated with ↑ed coagulation are seen in:
A. ↑ Protein C *(PGI Dec 06)*
B. ↑ Protein B
C. ↑ Anti thrombin III
D. Dysfibrinogenemia

424. Hypercoagulability due to defective factor V gene is called : *(AIIMS Nov. 03)*
A. Lisbon mutation
B. Leiden mutation
C. Antiphospholipid syndrome
D. Inducible thrombocytopenia syndrome

425. Most common inherited thrombotic disorder is :
A. Protein C deficiency *(PGI Dec. 05)*
B. Protein S deficiency
C. Factor V leiden mutation
D. Prothrombin gene mutation
E. tPA deficiency

426. Predisposing factor for arterial thrombosis:
A. AT III deficiency *(PGI Dec. 04)*
B. Protein S deficiency
C. Protein C deficiency
D. Homocystenemia

427. All of the following are aquired causes of Hypercoagulability, Except *(AI 2009)*
A. Infection
B. Inflammatory Bowel disease
C. Myeloproliferative disorders
D. Prolonged surgery > 1 hour

428. Causes of Deep venous thrombosis include all of the following, Except. *(AI 2009)*
A. Diabetes Mellitus
B. Oral contraceptives
C. Paroxysmal Nocturnal Hemoglobinuria (PNH)
D. Prolonged surgery

429. A patient is admitted with 3rd episode of deep venous thrombosis. There is no history of any associated medical illness. All of the following investigations are required for establishing the diagnosis *except* :
A. Protein C deficiency *(AIIMS Nov 2004)*
B. Antithrombin III deficiency
C. Antibodies to factor VIII
D. Antibodies to cardiolipin

### Antiphospholipid Syndrome

430. Anti Phospholipid Syndrome (APS) is associated with all of the following Except: *(AI 2008)*
A. Pancytopenia
B. Recurrent abortions
C. Venous thrombosis
D. Pulmonary hypertension

431. Antiphospholipid Antibody (APLA) syndrome is associated with all of the following except: *(AI 2010)*
A. Bleeding disorders
B. Thrombotic disorders
C. Coagulation disorders
D. Recurrent fetal loss

432. All of the following statements about Antiphospholipid Antibody Syndrome (APLAb) are true, Except :
A. Single titre of Anticardiolipin is diagnostic
B. Commonly presents with recurrent fetal loss

C. May cause pulmonary hypertension *(AI 2010)*
D. Warfarin is given as treatment

433. The following condition is not associated with an Anti-phopholipid syndrome: *(AI 2002)*
A. Venous thrombosis
B. Recurrent foetal loss
C. Thrombocytosis
D. Neurological manifestations

434. Patients with Antiphospholipid antibodies may manifest with any of the following, except: *(NBE)*
A. Venous thrombosis
B. Arterial Thrombosis
C. Hemolytic Anemia
D. Thrombocytosis

435. All are true regarding lupus anticoagulant except-
A. Thrombocytosis *(AIIMS Sep 96)*
B. Increased abortions
C. Rashes
D. Arterial thrombosis

436. All are true regarding Lupus anticoagulant, EXCEPT-
A. Increased abortions *(AIIMS Nov 93)*
B. Arterial thrombosis
C. Rashes
D. Increased PT

437. All of the following statements about Lupus Anticoagulant are true, Except. *(AI 2009)*
A. May present with an isolated prolongation of APTT
B. May present with Recurrent Abortions
C. May occur with minimal clinical manifestations
D. Thrombotic spells can be followed by severe life threatening haemmorrhage

438. Lupus anticoagulants may cause all of the following except: *(NBE)*
A. Recurrent abortion
B. False+ve VDRL results
C. Increase prothrombin time
D. Arterial thrombosis

439. Which of the following is recommended in a woman with Antiphospholipid Antibodies and history of prior abortions / still birth: *(AI 2010)*
A. Aspirin only
B. Aspirin + Low molecular weight Heparin
C. Aspirin + Low molecular weight Heparin + Prednisolone.
D. No Treatment

## Hemolytic Uremic Syndrome

440. All of the following statements are true about Hemolytic uramic syndrome except- *(AI 97, (NBE))*
A. Uraemia
B. Hypofibhrinogenemia
C. Thrombocytopenia
D. Positive coomb's test

441. Shigella associated hemolytic uramic syndrome is associated with all of the following except- *(NBE)*
A. Hyperkalemia
B. Thrombocytopenia
C. Neurological symptom
D. Renal micro thrombi

## Budd Chiari Syndrome

442. Commonest cause of Budd Chiari syndrome is-
A. Valve in the IVC *(AI 97)*
B. Hepatocellular carcinoma
C. Paroxysmal nocturnal hemoglobinuria
D. Renal cell carcinoma

443. Most common cause of Budd Chiari syndrome is:
A. Idiopathic *(AIIMS May 94)*
B. Valves in hepatic veins
C. Hepatocellular carcinoma
D. Thrombosis of hepatic veins

444. In Budd Chiari syndrome, the site of venous thrombosis is-
A. Infrahepatic inferior vena cava
B. Infrarenal inferior vena cava
C. Hepatic veins
D. Portal veins

445. What is the most common cause for Budd chiary syndrome- *(AIIMS Nov 2000)*
A. Right ventricular failure
B. PNH
C. Valve in hepatic veins
D. Polycythemia vera

## Blood Transfusion

446. Blood transfusion should be completed within how many hours of initiation: *(NBE)*
A. 4 hours
B. 6 hours
C. 8 hours
D. 12 hours

447. Shelf life of blood in a blood bank in CPDA buffer:
A. 21 days *(NBE)*
B. 30 days
C. 35 days
D. 42 days

448. Which of the following statements about Acute Hemolytic blood transfusion reactions is true:
A. Complement mediated Hemolysis is seen
B. Type III Hypersensitivity is responsible for most cases *(PGI June 04)*
C. rarely life threatening
D. Renal blood flow is always mainatained
E. No need for stopping transfusion

449. True about Blood transfusions (select two options) : *(PGI June 98)*
A. Antigen 'D' determines Rh positivity
B. Febrile reaction is due to HLA antigens

C. Anti-D is naturally occurring antibody
D. Cryoprecipitates contains all coagulation factors

450. MC blood transfusion reaction is- *(AI 2008)*
A. Febrile nonhemolytic transfusion reaction
B. Hemolysis
C. Transmission of infections
D. Electrolyte imabalnce

451. All of the following infections may be transmitted via blood transfusion, except: *(AI 2002)*
A. Parvo B-19
B. Dengue virus
C. Cytomegalo virus
D. Hepatitis G virus

452. All of the following viruses may be transmitted by blood transfusion Except: *(AIIMS May 09)*
A. Parvovirus B-19
B. Hepatitis G
C. Epstein Bar virus
D. Cytomegalovirus

453. Which of the following is the least likely complication after massive blood transfusion:
A. Hyperkalemia *(AIIMS May 09)*
B. Citrate toxicity
C. Hypothermia
D. Metabolic Acidosis

454. All of the following are major complications of massive transfusion, except: *(AI 2006)*
A. Hypokalemia
B. Hypothermia
C. Hypomagnesemia
D. Hypocalcemia

455. Which of the following investigations should be done immediately to best confirm a non matched blood transfusion reaction: *(AI 2010)*
A. Indirect Coomb's test
B. Direct Coomb's test
C. Antibody in patient's serum
D. Antibody in donor serum

456. Blood components products are: *(PGI Dec 05)*
A. Whole blood
B. Platelets
C. Fresh frozen plasma
D. Leukocyte reduced RBC

457. Platelets transfusion must be completed in how many hours after entering the bag: *(NBE)*
A. 1 hour
B. 2 hour
C. 3 hour
D. 4 hour

458. Shelf life of platelets in blood bank is:
A. 5 days *(NBE)*
B. 7 days
C. 10 days
D. 21 days

459. Half life transfused platelets is: *(NBE)*
A. 1 day
B. 2 days
C. 4 days
D. 8 days

460. Storage temperature of platelets is:
A. -4 degrees Celsius *(NBE)*
B. + 4 degrees Celsius
C. -20 degrees Celsius
D. + 20-24 degrees Celsius

461. Incorrect about platelet transfusion: *(NBE)*
A. Platelets carry the Rh antigen
B. Platelets bear the antigens of ABO system
C. Platelet products contain donor plasma
D. All of the above are true

462. Cryoprecipitate contains all except- *(AIIMS Nov 07)*
A. Factor VIII
B. Factor IX
C. Fibrinogen
D. VWF

463. Arterial blood Gas analysis in a bottle contaiing heparin causes a decrease in value of : *(NBE)*
A. $pCO_2$
B. $HCO_3^-$
C. pH
D. All of the above

## Miscellaneous

464. Hb concentration at birth is normally:
A. 10 g/dL *(NBE)*
B. 8 g/dL
C. 12 g/dL
D. 14g/dL

465. 10. Anaemia in an infant aged 9 months can be defined as: *(NBE)*
A. < 14g/dL
B. < 11 g/dL
C. < 8 g/dL
D. < 12 g/Dl

466. Anaemia in a child aged 12 years can be defined as:
A. < 11 g/dL *(NBE)*
B. < 12 g/dL
C. < 15g/dL
D. < 13 g/dL

467. A patient with blood pressure of 90/60 mm Hg presents with pronounced cyanosis. Blood drawn from peripheral veins is observed to be chocolate brown in colour. The most likely diagnosis is:
A. Methaemoglobinemia
B. Hypovolemic shock
C. Cardiogenic shock
D. Hemorrhagic shock

468. Low Erythropoetin levels are seen in: *(NBE)*
   A. Aplstic Anemia
   B. Renal failure
   C. Obesity
   D. Hepatoma

469. While handling a febrile neutropenic patient all are essential *except* : *(AI 1998)*
   A. Repeated hand washing of hospital person
   B. White cell infusion
   C. Prophylactic antibiotic
   D. Colony stimulating factor for macrophages

470. All of the following are Preleukemic conditions, Except: *(AIIMS 2011)*
   A. Paroxysmal Nocturnal Haemoglobinuria (PNH)
   B. Paroxysmal Cold Haemoglobinuria (PCH)
   C. Myelodysplasia
   D. Aplastic anemia

471. Splenomegaly is least likely to be associated with:
   A. Chronic Myeloid Leukemia (CML)
   B. Polycythemia Rubra Vera *(AIIMS Nov 2010)*
   C. Myelofibrosis
   D. Primary Thrombocytosis

472. Which of the following drugs is recommended for the treatment of Heparin Induced thrombocytopenia
   A. Abciximab *(AI 2010)*
   B. Lepirudin
   C. Warfarin
   D. Alteplase

## ANSWERS, REFERENCES, EXPLANATIONS AND RELEVANT HIGH YIELD FACTS

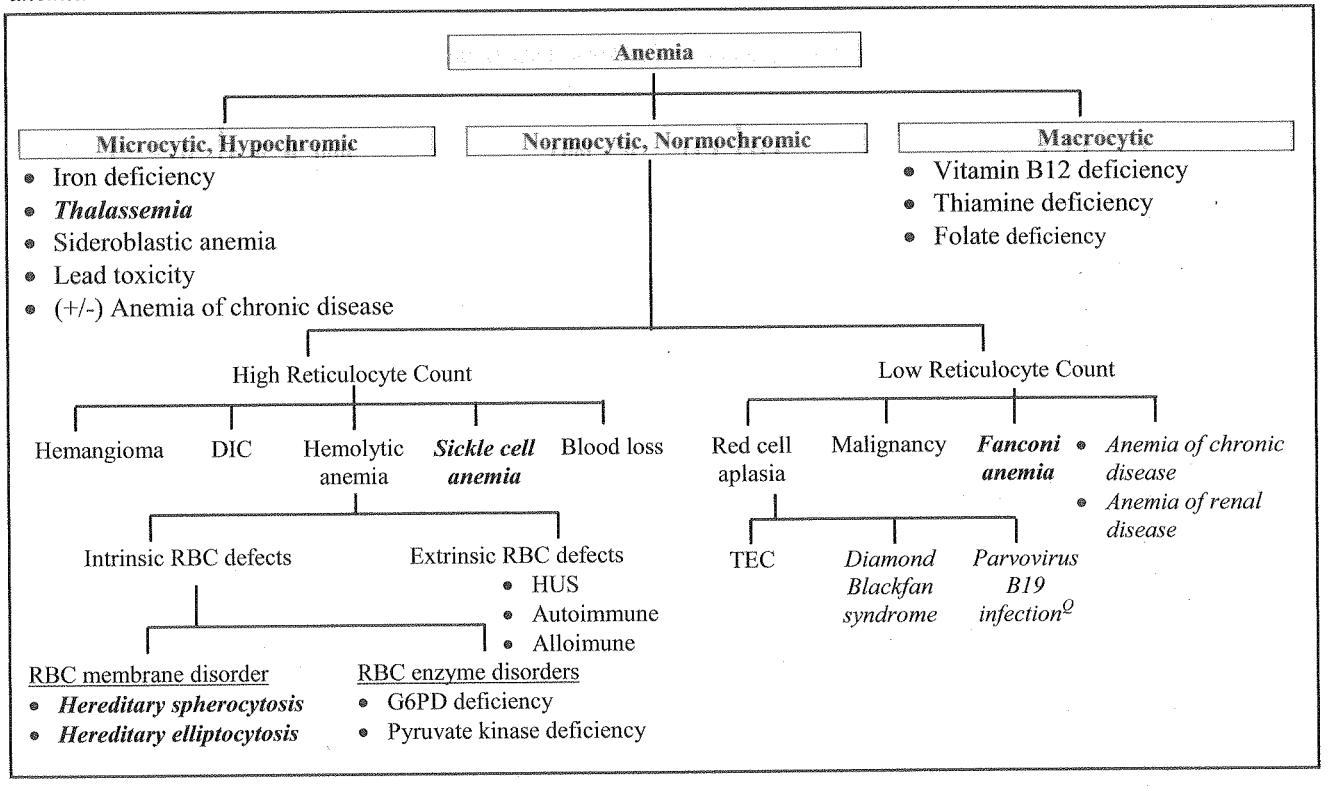
### Hypochromic Microcytic Anemias

#### Differential Diagnosis/Approach

**1. Answer is B (Thallassemia):** Harrison 18th/p 887, 889 *Harrisons 17th/663,665; Harrisons 16th/617,619; Board Review Series (BRS) Pediatrics (2004)/394*

***Thalassemia is associated with Hypochromic Microcytic Anemia.***

*Hereditary spherocytosis, sickle cell anemia and fanconi's anemia are associated with normocytic normochromic anemia*




Note:
*Anemia of chronic disease may present with microcytic hypochromic anemia

| Anemia of chronic disease: Normocytic Normochromic > Microcytic Hypochromic |
|---|

**2. Answer is D (Fanconi's anemia):** Harrison 18th/p 847, 848 *Refer previous question; Harrison 15th/ 663, Harrison 17th/ 631, 632; API edn 8th/ 796*

***Fanconi's anemia is a congenital disorder responsible for a form of aplastic anemia. It is a cause of normocytic normochromic anemia, and not microcytic hypochromic anemia.***

| Causes of microcytic hypochromic anaemia |
|---|
| • *Iron deficiency anaemia* |
| • *Thalassemia* |
| • *Sideroblastic anaemia* |
| • *Lead poisoning* |
| • *Anemia of chronic disease (+/-)* |

3. **Answer is D (Fanconi's Anemia):** Harrison 18th/p 847, 848 *Harrison 15th/ 663, Harrison 17th/ 631, 632; API edn 8th/ 796;*

*Refer previous question*

***Fanconi's anemia is congenital disorder responsible for a form of aplastic anemia. It does not produce a microcytic hypochromic picture. It causes a normocytic normochromic anemia.***

***Lead poisoning***

- Lead causes inhibition of several enzymes involved in haem synthesis including ALA synthetase and leads to sideroblastic anemia with a microcytic hypochronic anemia.
- The characteristic haematological features of lead poisoning include: *Kumar Clark 15th/ 416*

| |
|---|
| • Sideroblastic anemia $^{Q}$ |
| • Haemolysis $^{Q}$ |
| • Punctate basophilia $^{Q}$ |

4. **Answer is D and E (Sickle cell Anemia; Herediatry Spherocytosis):** Harrison 18th/p 848 *Harrison 17th/632*

*Sickle cell anemia and Hereditary Spherocytosis do not cause microcytic hypochromic anemia*

5. **Answer is B (Reduced Total RBC distribution width)**

***Microcytic Hypochromic Anemias are typically associated with a Normal or High Red Cell Distribution Width***

| Condition / Test (normal values) | Iron deficiency | Thalassemia | Sideroblastic anemia | Anemia of chronic disease |
|---|---|---|---|---|
| **Smear Microcytic (MCV<80)** | Microcytic hypochromic | Microcytic hypochromic | Microcytic hypochromic | Normocytic normochromic > Micro/hypochromic (but Micro/Hypo may be present) |
| **Serum iron (50-150µg/dl)** | Low (<30) | Normal | Normal | ↓ (<50) |
| **TIBC (300-360 µg/dl)** | High (>360) | Normal | Normal (Chandrasoma Taylor) | ↓ (<300) |
| **% Saturation (30-50%)** | < 10 (↓ed) | N or ↑ed (30-80) | N or ↑ (30-80) | ↓ (10-20) |
| **Ferritin (µg/l) (50-200 µg/L)** | < 15 (↓ed) | ↑ (50-300) | ↑ (50-300) | Normal or ↑ (30-200) |
| **Hemoglobin pattern** | Normal | Abnormal | Normal | Normal |
| **Free Erythrocyte Protporphrin** | ↑ed | Normal | ↑ed | ↑ed |
| **RDW** | ↑ed | Normal | Normal | Normal |

6. **Answer is D (Decreased Free Erythrocyte protoporphyrin):**

***Free Erythrocyte protoporphyrin is typically normal in Thalassemia while it is increased in other forms of Microcytic Hypochronic anemias like iron deficiency anemia, sideroblastic anemia and anemia of chronic disease.***

***Microcytic Hypochromic Anemias are typically associated with a Normal or High Red Cell Distribution Width***

| Condition / Test (normal values) | Iron deficiency | Thalassemia | Sideroblastic anemia | Anemia of chronic disease |
|---|---|---|---|---|
| **Free Erythrocyte Protporphrin** | ↑ed | Normal | ↑ed | ↑ed |

7. **Answer is B (Anemia of chronic disease):** Harrison 18th/p 848 *Harrison 17th/ 631*

*Hypochromic microcytic anemia with decreased serum iron and decreased TIBC is characteristic of anemia of chronic disease.*

Hypochromic microcytic anemia with ↓serum iron and ↑TIBC: iron Deficeincy Anemia
Hypochromic microcytic anemia with ↓ serum iron and ↓ TIBC : Anemia of Chronic disease

| Condition / Test (normal values) | Iron deficiency | Thalassemia | Sideroblastic anemia | Anemia of chronic disease |
|---|---|---|---|---|
| **Serum iron (50-150µg/dl)** | Low (<30) | Normal | Normal | ↓ (<50) |
| **TIBC (300-600 µg/dl)** | High (>360) | Normal | Normal (Chandrasoma Taylor) | ↓ (<300) |

**8. Answer is B & C(↓ TIBC;↑Ferritin):** Harrison 18th/p 848 *Harrison 17th/632*

***Anemia of chronic disease is associated with decreased TIBC and increased serum Ferritin while Iron deficiency anemia is associated with Increased TIBC and reduced serum Ferritin***

**Differential diagnosis of Microcytic Hypochromic Anemia**

| Parameters | Iron deficiency | Chronic Inflammatory |
|---|---|---|
| **Smear** | Microcytic hypochromic + target cell | Normocytic Normochromic > Microcytic Hypochromic |
| **Se Fe** | < 30 (↓) | ↓ (< 50) |
| ***TIBC*** | ***> 360 (↑)*** | ***↓ (< 300)*** |
| **Saturation** | < 10 (↓) | ↓ (10-20) |
| **Ferritin** | < 15 (↓) | ↑ (30-200) |
| **Free Erythrocyte Protporphrin** | ***↑ed*** | ***↑ed*** |

**9. Answer is A (Iron deficiency anemia):** Harrison 18th/p 847 *Harrison 16th edn /591; Harrison 17th edn /631*

***Hypochromic microcytic anemia with decreased serum iron and an increased total iron binding capacity (TIBC) suggests a diagnosis of 'iron deficiency anemia'***

| Parameter | Normal index | Patient in question | Inference |
|---|---|---|---|
| **Hb** | Male 14-18 g/dl<br>Female 12-16 g/dl | 7.8 g/dl | ↓ |
| **Serum Iron** | 50-150 µg/dl | 15 µg/dl | ↓ |
| **% Saturation** | 30-50% | - | - |
| **Serum Ferritin** | 50-200 µg/L | - | - |
| **Total iron binding capacity** | 300-600 µg/dl | 420 µg/dl | ↑ |
| **$HbA_2$** | 1.5 to 3.5% of total Hb. | 2.4% | N |
| **HbF** | <2% of total Hb. | 1-3% | N |

**Remember:**

- ***Hypochromic microcytic anemia with decreased serum iron and increased TIBC is iron deficiency anemia$^{Q}$***
- ***Hypochromic microcytic anemia with decreased serum iron and decreased TIBC is anemia of chronic disease$^{Q}$***

**Differential diagnosis of Microcytic Hypochromic Anemia**

| Parameters | Iron deficiency | Thalassemia | Sideroblastic | Chronic Inflammatory |
|---|---|---|---|---|
| **Smear** | Microcytic hypochromic + target cell | Microcytic hypochromic | Variable | Normocytic |
| **Se Fe** | < 30 (↓) | N | N | ↓ (< 50) |
| **TIBC** | > 360 (↑) | N | N | ↓ (< 300) |
| **Saturation** | < 10 (↓) | ↑ (30-80) | ↑ (30-80) | ↓ (10-20) |
| **Ferritin** | < 15 (↓) | ↑ (50-300) | ↑ (50-300) | ↑ (30-200) |

**10. Answer is C (Anemia of chronic disease):** *Refer table on Differential diagnosis of Hypochromic Microcytic Anemias*

***Decreased Serum Iron Levels, Decreased Transferrin Saturation and Increased Serum Ferritin Levels are typical features of Anemia of Chronic Disease.***

**11. Answer is C (Thalassemia):** *Harrisons 16th/589; Pediatric complaints and diagnostic dilemmas by Ludwig and Shah (2003)/275; Interpretation of Diagnostic tests by Wallach/400*

***Erythrocyte protoporphyrin levels are characteristically normal in Thalassemia***

*Free Erythrocyte Protoporphyrin is a useful screening test for microcytic hypochromic anemias. Free Erythrocyte protoporphyrin levels are increased in iron deficiency anemias, lead poisoning many cases of sideroblastic anemia and anemias of chronic disease. Erythrocyte protoporphyrin levels are normal in Thalassemias.*

| Parameter | Iron Deficiency | Lead Poisoning | Thalassemia trait | Chronic disease |
|---|---|---|---|---|
| Free Erythrocyte Protoporphyrin (FEP) | ↑ed | ↑ed | Normal | ↑ed |

**12. Answer is A (Iron Deficiency Anemia):** *Wintrobe's Hematology 12th/795,4; Harrison's Manual of Oncology (2007)/ 138*

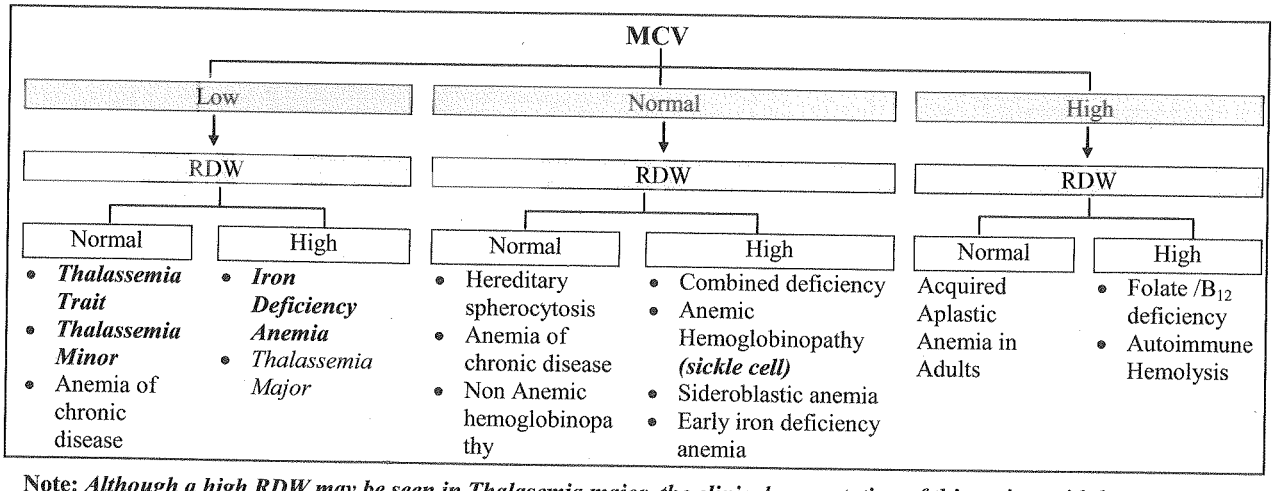
***Microcytic Hypochronic Anemia (↓MCV, ↓MCH) with an elevated Red cell distribution width*** *(Nomal RDW < 14.5%)* ***suggests a diagnosis of Iron deficiency anemia***

*'Among microcytic anemias, the red cell distribution width (RDW) distinguishes between iron deficiency anemia (↑RDW) and thalassemia (Normal RDW)'- Harrison's Manual of Oncology (2007)/138*

*'RDW is particularly useful in characterizing microcytic anemia, allowing to distinguish between uncomplicated iron deficiency anemia (High RDW, Normal to Low MCV) and uncomplicated heterozygous thalassemia (Normal RDW, Low MCV)' - Wintrobe's Hematology 12th/ - 4*

**Red Cell Distribution Width (RDW) and Evaluation of Anemia**

- *Red cell distribution width is a measure of anisocytosis and quantitates cellular volume heterogeneity*
- *An increased RDW suggests a state of increased anisocytosis as seen early in iron deficiency anemia*, and is especially useful in charachterizing microcytic anemias.
- MCV and RDW, together can be used to classify various types of anemias
- *The normal RDW is less than 14.5%*
- *Anisocytosis is an early and prominent finding in iron deficiency*, often detectable before significant microcytosis, hypochromia or anemia is apparent and hence *RDW tends to be elevated early in iron deficiency anemia. In contrast, anisocytosis tends to be mild or absent in Thalassemia.*
- *An increased RDW tends to be 90% to 100% sensitive for iron deficiency anemia (Although it is only 50% to 70% specific).*




**Note:** ***Although a high RDW may be seen in Thalasemia major, the clinical presentation of this patient with haemoglobin of 7.0 at the age of 16 years is not consistent with a diagnosis of Thalassemia major.***

**13. Answer is D (Anemia of Chronic Disease)**

*The Normal Red Cell Distribution Width (RDW) is less than 14.5 (Ranges from 11.5 to 14.5 but there is no known cause of decreased RDW). Normal MCV varies from 79-93.3 fl. The patient in question therefore has a Reduced MCV and a Normal RDW.* ***Low MCV along with Normal RDW suggests a diagnosis of Anemia of Chronic Disease.***

| Conditions with Reduced MCV and a Normal RDW |
|---|
| • *Anemia of Chronic Disease* |
| • *Beta Thalassemia Minor/Trait* |
| • *Alpha Thalassemia Minor/Trait* |
| • *Hemoglobin E Trait* |

*Normal RDW with low MCV is a feature of Thalassemia Trait and not Thalassemia Major.*
*Normal RDW with low MCV is a feature of HB-E trait (and not Hb-D Trait)*
*Iron Deficiency anemia is associated with elevated RDW*

*Note:*

| | |
|---|---|
| Thalassemia Trait | Low MCV ; Normal RDW |
| Anemia of Chronic Disease | Low MCV; Normal RDW or Normal MCV and Normal RDW |
| Iron Deficiency Anemia | Low MCV ; Increased RDW |

**14. Answer is A (Anisocytosis)**

***RDW is an indication of Anisocytois.***

*Red Cell Distribution Width (RDW) is a mathematical expression of size variation used to quantify anisocytosis.* The higher the RDW, the greater is the anisocytosis. RDW is increased in iron deficiency, and tends to be normal in thalassemia traits. Increased RDW may be an early indication of iron deficiency, where it may precede the onset of microcytosis.

**15. Answer is B (Iron deficiency):** Harrison 18th/p 847, 848 *Harrison 16th edn /589, 590; Harrison 17th edn /631, 632*

***Microcytic hypochromic anemia with increased levels of red cell protoporphyrin suggests a diagnosis of iron deficiency anemia.***

| Parameter | Normal | Patient | Inference |
|---|---|---|---|
| **Hb** | 13-18 g/dl | 6.5 | $\downarrow^{ed}$ (Anemia) |
| **MCV** | 86-98 $\mu m^3$ | 65 | $\downarrow^{ed}$ (microcytosis) |
| **MCH** | 28-33 g/dl | 15 | $\downarrow^{ed}$ (hypochromia) |

**Protoporphyrin** is an intermediate in the pathway of heme synthesis. Under conditions in which synthesis of heme is impaired, protoporphyrin accumulates within the red cell. Protoporphyrin levels thus determine a state of iron deficiency i.e. when there is inadequate iron to combine with protoporphyrin to form haem, the levels of protoporphyrin increases.

| Normal | Iron deficiency ($\uparrow$ed) |
|---|---|
| 30 µg/dl of red cells | 100 µg/dl of red cells |

- Microcytic hypochromic anemia with increased levels of red cell protoporphyrin is characteristic of iron deficiency anemia, but may also be seen in lead poisoning, anemia of chronic diseases and many cases of sideroblastic anemia.
- Red cell protoporphyrin will not be increased in Thalassemia as serum iron is normal or increased in them.

**16. Answer is A (Iron deficiency anemia) :** *Read text below*

| Parameter | Normal | Patient in question | Inference |
|---|---|---|---|
| Hb | 13 – 16 gm % | 3.8 gm % | Anemia |
| MCV | 79-93.3 fl | 58 fl | Microcytic |
| MCH | 26.7-31.9 pg/cell | 19.4 pg/cell | Hypochromia |
| **Inference** | **Hypochromic Microcytic Anemia** | | |

**The peripheral blood smear in patient with iron deficiency anemia:**

- Microcytosis
- Hypochromia
- Poikilocytosis & Anisocytosis (with increasing iron deficiency the RBC's become deformed and misshappen) -*Nelson*
- Normoblasts : 'The bone marrow reveals a mild to moderate increase in erythropoetic activity manifested by increased number of normoblasts. - *Robbins*

**Controversy 'Target cells' :**

According to Harrison's text, target cells are not seen with iron deficiency anemia, but CMDT states :
*'Severe iron deficiency will produce bizzare peripheral blood smear with severely hypochromic cells, target cells, hypochromic pencil shaped cells and occassionally small number of nucleated red blood cells." – CMDT 2004/464*

I would thus conclude that target cells are unusual with iron deficiency and when present should suggest either a globin chain production defect one of thallassemia or liver disease. Neverthless occasional target cells may be seen with iron deficiency anemia.

Excluding other three options :

**Acute Lymphoblastic anemia :** - Normocytic Normochromic anemia is seen
- Normoblasts in peripheral blood are unlikely

***Haemoglobin D disease :***
Heterozygos D is clinically silent
'Homozygous D produces a mild anemia with splenomegally. Severe anemia (Hb 3.8 gm%) will not result from HbD disease.
[There are 16 variants of HbD and only one D-Punjab (Los Angeles), in combination with HbS produces symptoms of sickle cell disease. This hemoglobin is seen in 1-3% of Western Indians and in some Europeans with a tie to India]
**Hereditary spherocytosis** is characterized by an increased osmotic fragility and is hence excluded.

17. **Answer is C (Thallassemia minor):** *Refer text below*

*The patient in question has a microcytic anemia (excludes Megaloblastic anemia) and has never required blood transfusion (excludes Thalassemia major). This patient may therefore have either an Iron deficiency anemia or Thalassemia minor.*
***Microcytic anemia (MCV 55 fl) with a normal RBC count (4.5 x $10^{12}$/L) favours a diagnosis of Thalassemia minor over Iron Deficiency Anemia.***

*Thalassemia minor is typically characterized by a normal or elevated RBC count while in Iron deficiency anemia the RBC count is significantly reduced.*

**Approach**

| Parameter | Normal values | Patient values | Interpretation | Mentzer's Index | *A value of Mentzer index below 13 is highly predictive of Thalassemia* |
|---|---|---|---|---|---|
| **RBC count** | (M) 4.3 – 5.6 x $10^{12}$/L<br>(F) 4.0 – 5.2 x $10^{12}$/L | 4.5 x $10^{12}$/L (F) | *Normal range* | *MCV/RBC Count* | |
| **MCV** | 79 – 93.3 fl | 55 fl | *Reduced MCV (Microcytic Anemia)* | *55/4.5 =12.22 (<13)* | |

**The patient in question has a microcytic anemia with a normal Red cell count and has never required a blood transfusion**

*The patient in question may have either an Iron Deficiency Anemia or Thalassemia Minor*

**Megaloblastic Anemia** *can be excluded since the MCV is reduced*
**Thalassemia Major** *can be excluded since the patient has never required blood transfusion to the age of 30*

**Special parameters to distinguish Thalassemia Minor from Iron Deficiency Anemia**

| Special Parameters | Thalassemia Minor | Iron Deficiency Anemia |
|---|---|---|
| ***Red Cell Distribution width (RDW)*** | *Normal* | *High* |
| ***Free Erythrocyte Protoporphyrin (FEP)*** | *Normal* | *High* |
| ***Red Blood Cell Count*** | *Normal or Increased* | *Reduced* |

**Several Red Cell indices** may help to distinguish Iron deficiency Anemia from Thalassemia minor and various formulas have been evolved to make this distinction.
*The most commonly used index is the **Mentzer Index**, which utilizes MCV and Red cell Count.*

| *Mentzer Index = MCV / Red Cell Count* |
|---|

*Mentzer Index* utilizes the finding that the Red Cell counts are higher in Thalassemia minor in comparison to Iron deficiency anemia to distinguish these two causes of microcytic hypochromic anemia.

| | |
|---|---|
| *Since RBC count is higher in Thalassemia minor the Mentzer Index will be low.*<br>*Since RBC count is lower in Iron deficiency anemia the Mentzer Index will be high* | *Mentzer Index = MCV / RBC Count* |

| Index | Thalassemia Minor | Iron Deficiency Anemia |
|---|---|---|
| *Mentzer Index (MCV/RBC count)* | *< 13* | *> 13* |

*A value of Mentzer index below 13 is highly predictive of Thalassemia.*

**18. Answer is C (Haemochromatosis):** *Harrison 16th edn /2259, 663, 2302, 590; Harrisons 17th edn /2432, 2433, 631*

***None of the conditions other than haemochromatosis present with an increased serum iron along with an increased serum ferritin and percent saturation of transferrin.***

**Haemochromatosis** is a disorder of iron storage in which an in appropriate increase in intestinal iron absorption results in deposition of excessive amounts of iron in parenchymal cells with eventual tissue damage and impaired function of organs.

Diagnosis is established after assessment of parenchymal iron stores.

| Parameter | Haemochromatosis | Iron deficiency anemia | Anemia of chronic disease |
|---|---|---|---|
| Serum iron | Increased | Low | Decreased |
| % saturation of transferrin | ↑ed : > 50% saturation | ↓ed : < 10 % saturation | Decreased |
| Serum ferritin | ↑ed | Decreased | Normal or Increased |

**Lead poisoning may present with :**

- A normocytic normochromic anemia ♀ with basophilic stippling ♀.
- Microcytic hypochromic picture may be seen
- Elevated free erythrocyte protophyrin may be seen

## Iron Deficiency Anemia

**19. Answer is A (Iron Deficiency Anemia):** *Manual of clinical hematology (Lippincott Williams & Wilkins)2010/ 152*

***Mentzer index more than 13 suggests a diagnosis of iron-deficiency anemia.***

**Mentzer Index** (Described in 1973 by Mentzer)

- The Mentzer index is used to help in differentiating iron deficiency anemia from beta thalassemia.
- The index is calculated as the quotient of the mean corpuscular volume (MCV, in fL) divided by the red blood cell count (RBC, in Millions per microLiter)
- If the Mentzer Index is less than 13, thalassemia is said to be more likely.
- If the Mentzer Index is greater than 13, then iron-deficiency anemia is said to be more likely.

*Principle: In iron deficiency, the marrow cannot produce as many RBCs and they are small (microcytic), so the RBC count and the MCV will both be low, and as a result, the index will be greater than 13. Conversely, in thalassemia, which is a disorder of globin synthesis, the number of RBC's produced is normal, but the cells are smaller and more fragile. Therefore, the RBC count is normal, but the MCV is low, so the index will be less than 13*

- In practice, the Mentzer index is not a reliable indicator and should not, by itself, be used to differentiate the two conditions

**20. Answer is A (Chronic renal failure):** *Refer text below*

*Chronic Renal failure causes a normocytic normochromic anemia due to deficiency of Erythropoetin.*
*Iron deficiency anemia may develop in patients with chronic renal failure who are on dialysis because of the blood lost in the dialysis equipment.*

***However, chronic renal failure remains the single best answer of exclusion.***

**Causes of iron deficiency anemia**

| Blood Loss | | Diet |
|---|---|---|
| • Gastrointestinal bleeding<br>- Hemorrhoid<br>- Angiodysplasia of the colon<br>- Hereditary, hemorrhagic, teleangiectasia syndrome (Osler-Weber-Rendu syndrome)<br>- Peptic ulcer<br>- Nonsteroidal, anti-inflammatory drugs<br>- Oral anticoagulation<br>- Hiatal hernia<br>- Meckel diverticulum<br>- Diverticulosis of the colon<br>- Intestinal polyps<br>- ***Carcinoma***<br>- Inflammatory bowel disease<br>- Hookworm: Nector Americanus, Ancylostoma duodenale<br>- Shistosoma: S. Mansoni, S. hematobium<br>- Trichuris | • Menstruation<br>• Frequent blood donations<br>• Erythrocyturia: bladder neoplasm<br>• Hemoglobinuria<br>- Paroxysmal, nocturnal hemoglobinuria<br>- Erythrocyte fragmentation in prosthetic heart valves<br>• Factitious anemia<br>• Intravenous and intra-arterial drug abuse<br>• ***Hemodialysis***<br>• Nosocomial blood loss due to frequent venisection | **Malabsorption**<br>• Achlorhydria<br>• Chronic, atrophic gastritis<br>-Gastric resection and bypass<br>-Vagotomy<br>-Intestinal bypass operations<br>• ***Celiac disease (=nontropical sprue)***<br>• Tropical sprue<br>**Increased iron requirements**<br>• Pregnancy and lactation<br>• Growth |

**21. Answer is C (Hookworm infection):** *Refer text below*

***The indices of the patient in question suggests a diagnosis of Microcytic Hypochromic anemia. The single best cause for his anemia is a Hookworm infection which causes an iron deficiency anemia due to persistant gastrointestinal blood loss.***

**Phenytoin and Blind loop syndrome** are causes for Macrocytic anemias

**CRF** causes a normocytic normochromic anemia.

**22. Answer is D (Alkaline pH):** Harrison 18th/p 845 *Harsh Mohan 4th/316, Harrison 17th/629, 630*

***Iron absorption is increased by acidic pH of stomach and not by an alkaline pH.***

**Factors that enhance / reduce iron absorption**

| | Enhanced absorption | Reduced absorption |
|---|---|---|
| Dietary factors | • Increased heme iron<br>• Increased animal food<br>• ***Ferrous iron salts*** | • Decreased heme iron<br>• Decreased animal foods<br>• Ferric iron salts |
| Luminal factors | • ***Acid pH***<br>• Low molecular weight soluble chelates | • ***Alkaline pH (e.g. pancreatic secretion)***<br>• Insoluble iron complexes |
| Systemic factors | • ***Iron deficiency***<br>• Increased erythropoesis<br>• ***Pregnancy***<br>• ***Hypoxia*** | • ***Iron overloaded***<br>• Decreased erythropoiesis<br>• Inflammatory disorders |

**23. Answer is A (Increased TIBC decreased serum Ferritin) ;** Harrison 18th/p 847 *Harrison 16th edn /592; Harrison 17th edn /631*

***Iron deficiency anemia is associated with increased TIBC, decreased serum Ferritin.***

| Serum iron | TIBC | Transferrin saturation | Ferritin |
|---|---|---|---|
| Serum iron reflects the amount of circulating iron bound to transferrin | TIBC is an indirect measure of the circulating transferrin | This is a measure of transferrin saturated with iron and is given by : Serum iron/TIBC x 100 | Within cells iron is stored complexed to protein as ferritin |
| Normal range of serum iron is 50 to 150 µg/dL | Normal range for TIBC is 300 to 360 µg/dl | Normal transferrin saturation ranges between 25 – 50%. | Normal values for serum ferritin depend on age and gender Adult males 100mg/L Adult females 30 µg/L. |
| Iron deficiency anemia is associated with ***decreased serum iron levels of < 30 µg/dL*** | Iron deficiency anemia is associated ***with increased TIBC > 360 µg/dl*** | Iron deficiency anemia is associated with ***decreased transferrin saturation below 18%*** (*< 10%; H16th / table*) | Iron deficiency states are associated with ***decreased serum ferritin to <15 µg/dl.*** |

**24. Answer is C (Decreased TIBC):** *Repeat*

***Total Iron Binding Capacity (TIBC) is typically increased in Iron Deficiency Anemia.***
*Iron Deficiency Anemia is a Microcytic Hypochromic Anemia characterized by Decreased Serum Iron, Decreased Serum Ferritin, Decreased Transferrin Saturation. The Total Iron Binding Capacity (TIBC), Red Cell Distribution Width (RDW) and Free Erythrocyte Protoporphyrin levels are typically increased.*

**25. Answer is B (Increased TIBC):** *Refer Differential Diagnosis of Iron Deficiency Anemia; Harrison 18th/ 846,847*

***Iron Deficiency Anemia is a Microcytic Hypochromic Anemia characterized by Decreased Serum Iron, Decreased Serum Ferritin, Decreased Transferrin Saturation and Increased TIBC.***

**26. Answer is B (Decrease in serum ferritin):** *Harrison 16th edn /630; Chandrasoma Taylor 3rd/687*

***The first stage of iron deficiency is depletion of iron stores which is associated with a decrease in levels of serum ferritin levels only.*** *As long as some stores are still available, other indices viz. SI, TIBC, Red cell Protoporphyrin levels continue to be within normal limits.*

**27. Answer is D (Bone marrow iron is decreased earlier than serum iron):** Harrison 18th/p 846 *Harrison 17th/630*

***Serum levels of iron decrease after bone marrow iron is decreased.***

*As long as iron stores are present (serum ferritin, bone marrow iron), and can be mobilised, the serum iron, Total Iron Binding Capacity (TIBC) and red cell protoporphyrin levels remain within normal limits.*

***Iron deficiency anemia is associated with decreased ferritin levels and an increased TIBC.***

**28. Answer is B (Serum ferritin levels):** Harrison 18th/p 846 *Harrisons 16th/ 589; Harrison 17th edn / 630*

***Iron deficiency is best detected by measurement of serum ferritin.***

*'The test of choice for screening and diagnosis of iron deficiency is the serum ferritin. Ferritin is the storage protein of iron which correlates best with marrow iron stores. The test is highly sensitive and specific for the diagnosis of iron deficiency' - 'Primary care medicine' 6th/632*

*'Serum Ferritin indicates the iron store status and decreased serum ferritin is the first most sensitive and specific test for iron deficiency. The levels <15µg/L indicate depletion of iron stores and is diagnostis of iron deficiency (normal 15-300 µg/L)' - Essentials in Hematology & Clinical Pathology (JP) 2012/22*

**This is so because:**

- The first stage of iron deficiency is depletion of iron stores which is associated with a decrease in levels of serum ferritin levels only.
- As long as some stores are still available, other indices viz. SI, TIBC, Red cell Protoporphyrin levels continue to be within normal limits.
- As the patients are not anemic yet, RBC morphology is essentially normal.

**Remember**

- Iron is stored as Ferritin
- Ferritin found in circulation is in equilibrium with tissue ferritin
- Serum Ferritin levels fall as iron stores are depleted

**29. Answer is B (Serum ferritin):** *Harrison's 18th/847*

*Serum ferritin levels are the best marker for assessment of iron deficiency.*

**30. Ans. Answer is B (Serum Ferritin):** *Harrison's 18th/847*

*The most suitable test to assess iron status in serum Ferritin.*

*'Under steadystate conditions the serum ferritin is the most convenient laboratory test to estimate iron stores as the serum ferritin levels correlate with total iron body stores' - Harrison*

**31. Answer is A (Hypersegmented neutrophils):** *Harrison 18th/846, 847; Harrison 17th/630, 631; API 8th/794, 795, 796*

*Hypersegmented neutrophils are a feature of megaloblastic anemia, and not iron deficiency anemia.* ***This is such a characteristic finding, that a single cell with a nucleus of six or more lobes ♀ should raise immediate suspicion of a megaloblastic anemia*** *– Harrisons 16th/ 605*

- Iron deficiency anemia is the commonest cause of anemia in India.
- It is a hypochromic, microcytic anemia and MCHC may well be less than 50% (Hypochromia).
- Initially cells tend to be microcytic and not hypochromic thus microcytosis precedes hypochromia. At lower haemoglobin levels both microcytosis and hypochromia become pronounced – *Harrison 16th/ 589*

**32. Answer is D (Decrease in absorption with improvement of symptoms):** Harrison 18th/p 848, 849 *Harrison 17th/632; Kelley's Essential of Internal Medicine 2nd/508*

*'Percentage absorption of iron falls progressively as iron deficiency is corrected'* -*Kelly's Essentials of Internal Medicine 2nd/508*

*'As the hemoglobin levels rise, erythropoietin stimulation decreases and the amount of iron reabsorbed is reduced'* .
*– Harrison 17th/632*

Oral therapy for iron deficiency anemia

- A dose of 300mg of elemental iron is given per day in divided doses
- ***300mg of elemental iron gives about 50mg of absorbed iron per day*** *(and not 100 mg of absorbed iron)*
- ***Typically the reticulocyte count should begin to increase in 4-7 days after initiation of therapy and peak at 1½ weeks*** *(not at 3-4 weeks)*
- ***Typically the Hb levels should be fully corrected within 1 month of initiating therapy in the absence of continuing blood loss*** *(and not after six months).*
- ***Treatment should not be stopped after normalizing of Hb, but continued for an additional 4 to 6 months to replenish body iron stores.***

**33. Answer is A (Intermittent Gastrointestinal Blood Loss):** *Harrison 18th / 849; Wintrobe's Clinical Hematology 13th/638; The Bethesda Handbook of Clinical Hematology 3rd/ 7*

*Intravenous Iron Therapy is reserved for patients with persistent (not intermittent) gastrointestinal blood loss who need iron on an on-going basis and in whom iron losses cannot be replenished by oral administration (due to significant losses from a high rate of bleeding)*

| Indications for Parenteral Iron Supplementation |
|---|
| • Inability to tolerate oral iron |
| • Poor compliance with oral iron |
| • Iron Malabsorption |
| • Persistent Gastrointestinal Blood Loss ( Iron losses cannot be replenished orally due to rate of bleeding) |
| • Unresponsiveness to oral Iron / Patients on Therapy with erythropoiesis-stimulating agents (ESA) |
| ○ Patients on ESA for Haemodialysis |
| ○ Patients on ESA For Anemia of Chronic Disease |

*Therapy with Erythropoiesis-Stimulating Agents (ESA) induces a large demand for iron – a demand that frequently cannot be met through oral iron absorption*

**34. Answer is C (Malabsorption related macrocytic anemia):**

*Iron Dextran is one of the preparations of iron available for parenteral iron replacement. It is only indicated to replenish iron stores and has no role in the treatment of Macrocytic anemias (Vitamin B12/Folic Acid Deficiency). Iron Dextran may be used in states associated with Iron Malabsorption.*

| Indications for Parenteral Iron Supplementation |
|---|
| • Inability to tolerate oral iron<br>• Poor compliance with oral iron<br>• Iron Malabsorption<br>• Persistent Gastrointestinal Blood Loss ( Iron losses cannot be replenished orally due to rate of bleeding)<br>• Unresponsiveness to oral Iron / Patients on Therapy with erythropoiesis-stimulating agents (ESA)<br>o Patients on ESA for Hemodialysis<br>o Patients on ESA For Anemia of Chronic Disease |

*Therapy with Erythropoiesis-Stimulating Agents (ESA) induces a large demand for iron – a demand that frequently cannot be met through oral iron absorption*

**35. Answer is A (Iron Dextran):** *Harrison 18th/ 849; Other Multiple References*

***The risk of anaphylaxis is maximally associated with Iron Dextran Preparations. Iron Dextran is now the only formulation that requires a test dose and premedication due to reported anaphylaxis reactions.***

Parenteral Iron Supplementation

- Parenteral Iron Supplementation may be used in special circumstances to treat iron deficiency in persons who have had suboptimal responses to oral therapy, who cannot tolerate oral iron supplements, or who have iron or blood loss that cannot be reconstituted adequately by using oral iron supplements alone

| Indications for Parenteral Iron Supplementation |
|---|
| • Inability to tolerate oral iron<br>• Poor compliance with oral iron<br>• Iron Malabsorption<br>• Persistent Gastrointestinal Blood Loss ( Iron losses cannot be replenished orally due to rate of bleeding)<br>• Unresponsiveness to oral Iron / Patients on Therapy with erythropoiesis-stimulating agents (ESA)<br>o Patients on ESA for Haemodialysis<br>o Patients on ESA For Anemia of Chronic Disease |

*Therapy with Erythropoiesis-Stimulating Agents (ESA) induces a large demand for iron – a demand that frequently cannot be met through oral iron absorption*

- Most patients who require parenteral iron receive it by intravenous infusion, because relatively large quantities of iron can be administered in single treatments.
- Intramuscular iron therapy has been largely abandoned because relatively little iron can be administered with each injection.
- Iron complexed to a carbohydrate moiety such as dextran, sucrose or gluconate is used for parenteral administration.

| Four formulations of parenteral iron are currently marketed in the United States |
|---|
| • *Iron dextran (Dex-Ferrum™, INFeD™),*<br>• *Sodium ferric gluconate in sucrose (Ferrlecit™),*<br>• *Iron sucrose (Venofer™), and*<br>• *Ferumoxytol (Feraheme)* |

- Although Iron Dextran continues to be the most commonly used parenteral iron formulation, iron dextran is increasingly being replaced in clinical practice with newer non-dextran formulations.
- The newer non-dextran formulations provide increased amount of elemental iron per dose which allows for more rapid correction of the iron deficit and increased compliance.
- The newer non-dextran formulations have fewer reported adverse events and Iron Dextran is now the only formulation that requires a test dose and premedication due to reported anaphylaxis reactions.

**36. Answer is C (Polycythemia vera):** Harrison 18th/p 846, 900, 3162 *Harrison 17th edn /630, 673 2430;(table 351-1)*

***Increased erythropoetin leads to increased haematopoasis and an increased demand for iron producing a state of iron deficiency. Polycythemia vera being a state of increased erythropoetin is a cause of iron deficiency rather than iron overload.***

**Iron overload states** *(Harrison 16th/336-1t)*

| Iron loading anaemias | Chronic liver disease | Hereditary hemochromatosis | Dietary iron overload |
|---|---|---|---|
| • *Thalassemia major*<br>• *Sideroblastic anaemia*<br>• *Chronic hemolytic anaemias*<br>• *Transfusional and parenteral iron overload* | • *Hepatitis C*<br>• *Alcoholic cirrhosis (advanced)*<br>• *Non alcoholic steatohepatitis*<br>• *Porphyria cutanea tarda*<br>• *Post portocaval shunting* | | |

## Anemia of Chronic Disease

**37. Answer is C (Normal or increased serum ferritin):** *Refer table 'Differential diagnosis of Microcytic Hypochromic Anemia'*

***Anemia of chronic disease is associated with normal or increased serum Ferritin.***

*Anemia of chronic disease is associated with decreased serum iron, decreased TIBC, decreased % saturation and normal or increased serum Ferritin levels.*

| Condition / Test (normal values) | Iron deficiency | Thalassemia | Sideroblastic anemia | Anemia of chronic disease |
|---|---|---|---|---|
| **Smear** | Microcytic hypochromic | Microcytic hypochromic | Microcytic hypochromic | Normocytic normochromic > Micro/hypochromic (but Micro/Hypo may be present) |
| **Serum iron (50-150µg/dl)** | Low (<30) | Normal | Normal | ↓ (<50) |
| **TIBC (300-360 µg/dl)** | High (>360) | Normal | Normal (Chandrasoma Taylor) | ↓ (<300) |
| **% Saturation (30-50%)** | < 10 (↓ed) | N or ↑ed (30-80) | N or ↑ (30-80) | ↓ (10-20) |
| **Ferritin (µg/l) (50-200 µg/L)** | < 15 (↓ed) | ↑ (50-300) | ↑ (50-300) | Normal or ↑ (30-200) |
| **Hemoglobin pattern** | Normal | Abnormal | Normal | Normal |
| **Free Erythrocyte Protporphrin** | ↑ed | Normal | ↑ed | ↑ed |
| **RDW** | ↑ed | Normal | Normal | Normal |

**38. Answer is B (Anemia of Chronic Disease):** *Repeat*

***Microcytic anemia (MCV < 80) with decreased Serum Iron and decreased TIBC suggest a diagnosis of Anemia of Chronic Disease.***

| | |
|---|---|
| Hypochromic microcytic anemia with ***↓Serum Iron and ↑TIBC*** | *Iron Deficeincy Anemia* |
| Hypochromic microcytic anemia with ***↓ Serum Iron and ↓ TIBC*** | *Anemia of Chronic disease* |

**39. Answer is B (Decreased Ferritin):** *Harrison 18th/849; 15th/ 665; 16th/ 590, 591; 17th edn / 633*

*Anemia of chronic disease is characterised by a block in delivery of iron from the reticulo-endothelial system to the erythroid progenitors. Consequently patients have normal to increased iron stores in the marrow and a normal or increased, ferritin level. Because of the block in delivery, serum iron levels fall and so does the TIBC and transferrin saturation.*

**Laboratory parameters in Anemia of chronic disease**

| Smear | SI (µg/dl) | TIBC (µg/dl) | Percent saturation (%) | Ferritin (µg/dl) | Hb pattern |
|---|---|---|---|---|---|
| Normocytic normochromic or Microcytic hypochronic | < 50 (↓) | 300 (↓) | 10-20 (↓) | 30-200 (↑) | Normal |

**Remember again:**

- *Low serum iron with an increased TIBC is : iron deficiency anemia*$^{Q}$
- *Low serum iron with a decreased TIBC is : anemia of chronic disease.* $^{Q}$

**40. Answer is A (Serum iron ↓, S. ferritin ↑, transferritin ↓):** *Harrison 18th/p 849 Harrison 17th/633*

*Anemia of chronic inflammations is associated with decreased serum iron, decreased transferrin levels (↓TIBC) and normal or increased ferritin levels.*

**41. Answer is A (Serum iron ↓ S. Ferritin ↑ and transferrin ↓):** *Refer table on Differential diagnosis of Hypochromic Microcytic Anemias*

*Anemia of Chronic Disease is associated with Decreased Serum Iron Levels, Decreased Total Iron Binding Capacity, Decreased Transferrin Saturation and Increased Serum Ferritin Levels.*

*The TIBC is the sum of all unfilled iron-binding sites on transferrin, and is measured as the total quantity of iron (umol/L) that saturates all of the iron-binding sites on transferrin after the addition of exogenous iron to serum. Hence TIBC is closely related to the concentration of Transferrin in the serum. TIBC is typically decreased in anemia of chronic disease while it is increased in Iron Deficiency anemia.*
*Transferrin saturation (TS) is the ratio of the serum iron concentration to the serum TIBC, expressed as a percentage. Transferrin saturation is decreased in both anemia of chronic disease and iron deficiency anemia.*

**42. Answer is C (Decreased serum ferritin level):** Harrison 18th/p 849 *Harrison 16th/ 590, 591; Harrison 17th edn / 633; Chandrasoma Taylor 3rd/ 388; See previous questions also.*

*Serum ferritin level is increased in patients with anaemia of chronic disease.*

**43. Answer is B (Increased total iron binding capacity):** Harrison 18th/p 849 *Harrison 15th edn /665, 666; Harrison 16th edn/590, 591, 592; Harrison 17th edn /633; Chandrasoma Taylor 3rd/ 388*

*Total iron binding capacity is decreased in patients with anaemia of chronic disease.*

## Anemia of Chronic Renal Failure

**44. Answer is C (Dialysis worsens anemia of renal failure):** *Harrison 18th/p 850; Williams Hematology /452*

*Dialysis has little effect with regard to correcting the anemia of chronic renal failure.*
*Dialysis may improve the anemia of renal disease but it does not usually worsen it.*

Anemia of chronic renal failure

- *It is normocytic normochromic, hypoproliferative anemia*
- ***The level of anemia correlates with the severity of renal failure***
- *The anemia is primarily due to a failure to produce adequate amounts of Erythropoetin and a reduction in red cell survival.*
- *Patients usually present with normal serum iron, TIBC & ferritin levels*
- ***Erythropetin therapy is the mainstay of treatment (improves symptoms)***
- ***Dialysis per se tyopically has little effect with regard to correcting the anemia.***
  ***Peritoneal dialysis (ambulatory) usually improves anemia while hemodialysis may cause an associated iron deficiency anemia.***

**45. Answer is A (Decreased Erythropetin Production):** Harrison 18th/p 850 *Harrison 17th/633*

***The Anemia of chronic renal failure is primarily due to failure to produce adequate amounts of Erythropetin (EPO) and a reduction in red cell survival.***

**Anemia in chronic renal failure is usually not caused by iron deficiency**
Patients with anemia of chronic renal failure usually have normal levels of serum iron, serum TIBC and serum ferritin. *Iron deficiency anemia may however be seen in some patients with CRF who are maintained on chronic hemodialysis due to loss through the dialysis procedure.*
**Anemia of chronic renal failure is not caused by deficiency of vitamin B12 or folate deficiency**
**Anemia of chronic renal failure is not caused by a Hypoplastic bone marrow.**

## Sideroblastic Anemia

**46. Answer is B (Decreased transferrin saturation):** Harrison 18th/p 848 *Harrison 16th/ 589, 590; Harrison 17th edn /632; Chandrasoma Taylor 3rd/ 388*

***High or normal transferrin saturation is found in sideroblastic anaemia.***

**Sideroblastic anemia:** is an uncommon form of anemia characterized by the presence of a large no of sideroblasts in the bone marrow.

*Sideroblasts: are erythroid precursors with demonstrable Cytoplasmic iron Q.*
*Ring sideroblasts Q* are normoblasts in which the amount of iron is so greatly increased that it appears as Cytoplasmic granules arranged in a complete ring around the nucleus.

**Defect:** *There is a defect in incorporating iron into the haemoglobin molecule within the erythrocyte.*

**Laboratory parameters in Sideroblastic Anemia:**

| Smear | SI (µg/dl) | TIBC (µg/dl) | Saturation | Ferritin (µg/dl) | Marrow |
|---|---|---|---|---|---|
| Hypochromic microcytic or *Dimorphic Q picture | Normal or ↑ed | Normal | Normal or ↑ed | Increased | Sideroblasts |

***Dimorphic Q**: mixture of hypochromic microcytic and macrocytic erythrocytes*

**47. Answer is B (Sideroblastic anemia) :** Harrison 18th/p 848 *Harrison 17th edn /632; Repeat*

***The association of Increased serum iron, Increased percent saturation and Increased serum ferritin is consistent with the presentation of Sideroblastic anemia..***

***The TIBC in Sideroblastic anemia is usually normal (Harrison), but it may also be decreased or low. Sideroblastic anemia is the single best answer of choice.***

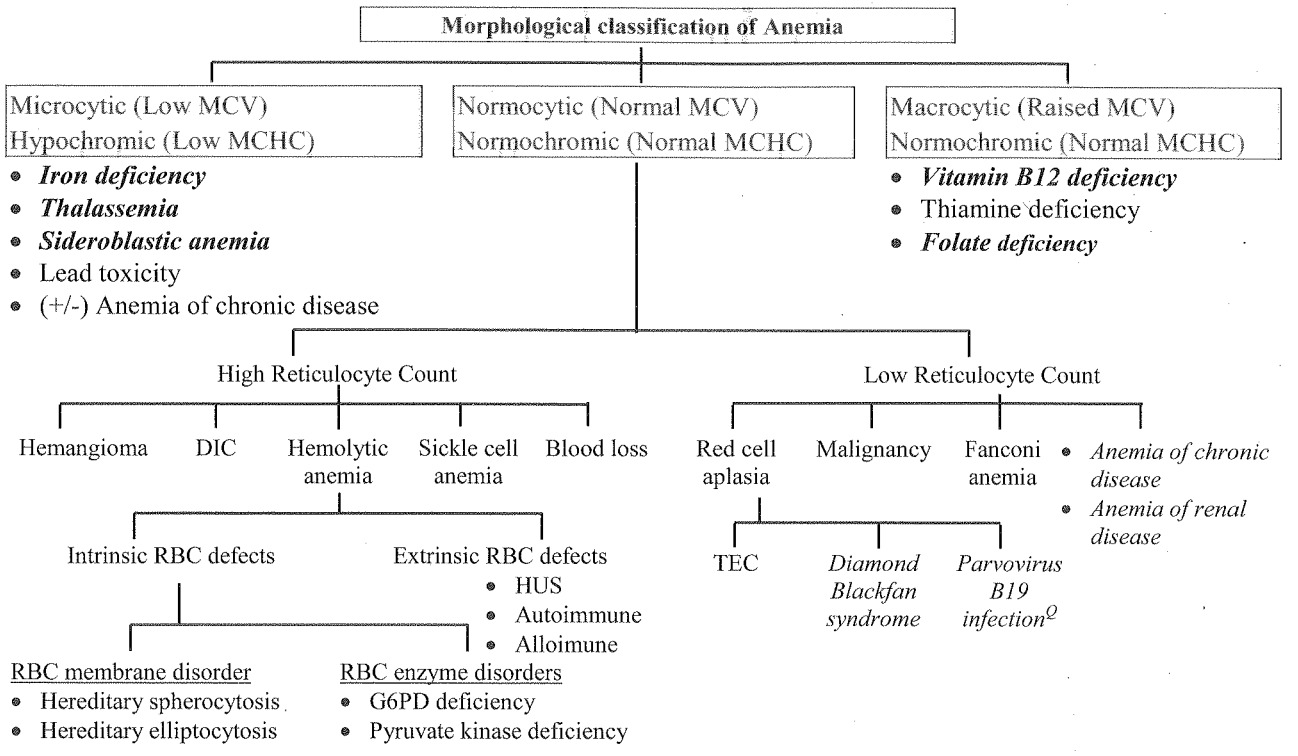
## Megaloblastic Anemia

**48. Answer is B (Vitamin B12 and Folic acid deficiency):** *Repeat*

***Raised MCV (Macrocytic) and normal MCHC (Normochromic) suggests a diagnosis of Macrocytic Normochromic anemia seen most characteristically with vitamin B12 and Folic acid deficiency.***

*Iron deficiency anemia, Beta-thalassemia and Sideroblastic anemia are all Microcytic (Low MCV) Hypochromic (Low MCHC) anemias.*

| MCV (Mean Corpuscular Volume) | MCHC (Mean Corpuscular Hb concentration) |
|---|---|
| • Mean Corpuscular Volume refers to the average size of the RBC (volume).<br>• MCV is usually expressed in femtoilitres (fl)<br>• Normal MCV varies from 79.0 to 93.3 fl *(H 18th/3587)*<br>Raised MCV: Macrocytic<br>Normal MCV: Normocytic<br>Reduced MCV: Microcytic | • Mean Corpuscular Haemoglobin Concentration (MCHC) refers to the average concentration of Hb in the RBC (MCHC describes the colour of the RBC)<br>• MCHC is usually expressed in pg/dl<br>• Normal MCHC varies from 32.3 to 35.9 pg/dl *(H 18th/3587)*<br>Raised MCHC: Hyperchromic<br>Normal MCHC: Normochromic<br>Reduced MCHC: Hypochromic |




| | |
|---|---|
| Most of the anemias mentioned in this section have a normal MCV & MCHC.<br>However, Macrocytic (↑MCV) or Microcytic (↓MCV) and Hypochromic (↓MCHC) cases may all be encountered | Macrocytic Anemia is characterized by an increase in the MCV<br>The Haemoglobin content increases proportionately to the erythrocytic voume.<br>***Therefore as a rule macrocytic anemia is normochromic.*** |

**49. Answer is B (Copper deficiency):** Harrison 18th/p 862 *Nelson 15th/ 408; Harrison 14th/ 657, Harrison 15th/ 679, 675, 468, Harrison 17th/643;(table 100-1); Chandrasoma Taylor 3rd/ 379, 382*

*Cu deficiency has not been mentioned to cause megaloblastic picture. It causes a normocytic hypochromic picture.*

- **Orotic acid** is an intermediate metabolite in the synthesis of pyrimidines. Orototic aciduria is a rare disorder in children, resulting from block of further metabolism of orotic acid.
  ***Affected children have megaloblastic anemia that is unresponsive to Vit C, Vit B12 and folic acid.***
- **Thiamine deficiency** may be associated with 'thiamine responsive anemia'. In the untreated state this ***gives rise to a megaloblastic anemia***. - *Nelson 15th/173*
- **Liver disease** may give rise to ***megaloblastic anemia***, by interferring with storage and metabolism of fat soluble vitamin $B_{12}$.

| Causes of Macrocytic anemia |
|---|
| 1. Vit. $B_{12}$ deficiency |
| 2. Folic acid deficiency |
| 3. Orotic aciduria |
| 4. Nitrous oxide inhalation |
| 5. Liver disease |
| 6. Hypothyroidism |
| 7. Thiamine deficiency |

**50. Answer is D (Amoxycilline):** Harrison 18th/p 862 *Harrison 14th/ 426, 633, Harrison 15th/ 675; Harrison 16th/ 601; Harrison 17th/643*

*All options other than Amoxycylline are mentioned as causes for megaloblastic anemia.*

| **Megaloblastic Anemia is caused by :** | |
|---|---|
| 1. Phenytoin [Q]<br>2. Primidone [Q]<br>3. Phenobarbitone [Q]<br>4. Nitrous oxide | 5. Folate antagonists :<br>(inhibiters of dehydrofolate reductase) - *Harrison 14th / 653*<br>- Methotrexate [Q] - Pyrimethamine [Q]<br>- Pentamidine [Q] - Triamterine [Q]<br>- Triamethoprim [Q] - Cotrimaxazole [Q] |
| ***Also, Drugs that inhibit DNA synthesis may cause Megaloblastic Anemia*** - *Harrison 14th/ 653* | |
| - **Purine Antagonist** : 6-Mercaptopurine, Azathioprine [Q]<br>- **Pyrimidine antagonist** : 5FU, cystosine arabinose [Q]<br>- **Others** : Procarbazine, hydroxyurea, acyclovir, zidovudine. [Q] | |

**51. Answer is A (Inadequate dietary intake):** *Harrison 16th/603*

***Folic acid deficiency most commonly results from either decreased dietary intake or increased metabolic demand. Amongst the options provided decreased dietary intake is the single best answer.***

Megaloblastic anemia

| Cobalamine deficiency | Folate deficiency |
|---|---|
| Most common cause is Malabsorption<br>*'The dietary intake of cobalamine is more than adequate for body's requirement except in complete vegetarians and their breast fed infants. **Thus deficiency of cobalamine is almost always due to malabsorption'** – Harrison 16th/603* | Most common cause is either decreased dietary intake or increased metabolic demand.<br>*The dietary intake of folic acid is marginal in many parts of the world. Furthermore because the body's stores of folate are low, **folic acid deficiency can arise rather suddenly during periods of decreased dietary intake or increased metabolic demand'** – Harrison 16th/603* |

**52. Answer is B (Bacterial overgrowth):** *Harrison 16th/1773-74; Love&Bailey 23rd/1031*

*Vitamin $B_{12}$ deficiency in blind loop syndrome is not due to defect in the absorption process of vit $B_{12}$ but due to competitive uptake of vit $B_{12}$ by colonizing bacteria* and hence decreased availability of vit $B_{12}$ for absorption.
***In Blind loop syndrome, malabsorbtion occurs secondary to bacterial overgrowth.***

The possible mechanism causing malabsorption are :

1. *Bacterial deconjugation of bile salts :* In contrast to conjugated bile salts, unconjugated bile salts may be absorbed in the proximal small bowel resulting in decreased intraluminal concentration of bile salts in Jejunum. This leads to impaired micelle formation and hence fat malabsorption.
2. Utilization of vit $B_{12}$ by bacteria: The impaired absorbtion of vit $B_{12}$ is not related to above disturbed bile salt metabolism, but appears to be due to uptake of vit $B_{12}$ by microorganisms i.e. competition for vit $B_{12}$ by bacteria.
3. Injury to the mucosal absorptive surface.

*Remember:*
- Blind loop in the *upper intestine* : defect is chiefly of Fat malabsorption / Steatorrhea [Q]
- Blind loop in the *lower intestine* : There is Vitamin $B_{12}$ deficiency / Megaloblastic anemia [Q]

**53. Answer is B (Homocystinemia):** *Harrison 18th/p 594, 595, 3218; 16th/ 1422, 1423, 403; 17th/ 441, 442, 2470, 2473*

***All options other than homocyctinemia have been clearly mentioned as causes of thiamine deficiency.***

**Causes of thiamine deficiency** – *Harrison*

1. **Malnutrition** [Q]
2. **Dietry habits** particularly in the far-east where *polished rice* [Q] deficient in thiamine is the major dietry component.
3. **Alcoholics and food faddists** [Q]**:** *In western nations the wide spread use of thiamine enriched flour limits the presence of deficiency primarily to alcoholic and food faddists – Harrison 15th/ 14th*
4. **Chronic heart failure** [Q]**:**

- The measurement of thiamine pyrophosphate effect can biochemically quantitate thiamine stores.
- An elevated TPPE indicative of thiamine deficiency has been found in 20 to 90% of patients with chronic heart failure.
- The deficiency appears to result from both, reduced dietry intake and a diuretic induced increase in urinary excretion of thiamine - *Harrison*

**54. Answer is B (Pernicious Anemia):** *Robbin's 7th/639*

***Deficiency of Intrinsic factor leads to a specific form of vitamin B12 deficiency megaloblastic anemia called 'Pernicious Anemia'.***
*Pernicious Anemia also known as Addison's Anemia is a megaloblastic anemia due to deficiency of intrinsic factor (secreted by parietal cells of gastric mucosa) that is essential for vitamic B12 absorption.*

Note:
*'Intrinsic factor' was first described by castle & coworkers and hence intrinsic factor is also called Intrinsic factor of Castle.*

**55. Answer is A (Vitamin $B_{12}$):** *Harrison 17th /1878*

***Shilling's test is done to determine the cause of cyanocobalamine deficiency (Vitamin $B_{12}$).***

***Schilling test is abnormal in conditions that affect cobalamine absorption including Pernicious anemia, Chronic Pancreatitis, Bacterial overgrowth syndrome and Ileal dysfunction.***

| Conditions with Abnormal Schilling's Test (Abnormal Cobalamine Absorption) |
|---|
| *Pernicious anemia* |
| *Chronic Pancreatitis* |
| *Achlorhydria* |
| *Bacterial overgrowth syndrome* |
| *Ileal dysfunction* |

**Schilling Test:**

- Schilling test is performed to determine the cause of cobalamine malabsorption (Vit B12 malabsorption).
- Since cobalamine absorption requires multiple steps including gastric, pancreatic and ileal processes, the Schilling test can also be used to assess the integrity of these other organs.
- The Schilling test is performed by administering Co58-labeled cobalamin orally and collecting urine for 24h

> 1 mg of cobabmine is administed intramuscularly one hour after ingestion of the Radiolabelled cobalamine. This is done to ensure saturation of cobalamine binding sites in the liver as urinary excretion of cobalamine will reflect cobalamine absorption only provided that intrahepatic binding sites of cobalamine are fully occupied. Once intrahepatic binding sites of cobalamine are saturated all absorbed radiolabelled cobalamine will be excreted in urine

- The ***Schilling test may be abnormal (defined as less than 10 percent excretion in 24h) in conditions that affect cobalamine absorption including Pernicious anemia, Chronic Pancreatitis, Bacterial overgrowth syndrome and Ileal dysfunction.***
- The etiology for an abnormal Schilling test may be deduced by administering Co58-labeled cobalamin with intrinsic factor, pancreatic enzymes or after 5 day course of antibiotics. Differential Results of Schilling Test in various diseases associated with cobalamin malabsorption may thus help establish the diagnosis.

| Diagnosis | $^{58}$Co-Cbl | With Intrinsic Factor | With Pancreatic Enzymes | After 5 Days of Antibiotics |
|---|---|---|---|---|
| Pernicious anemia | *Reduced* | *Normal* | *Reduced* | *Reduced* |
| Chronic pancreatitis | *Reduced* | *Reduced* | *Normal* | *Reduced* |
| Bacterialovergrowth | *Reduced* | *Reduced* | *Reduced* | *Normal* |
| Ileal disease | *Reduced* | *Reduced* | *Reduced* | *Reduced* |

**56. Answer is A (Intrinsic factor deficiency):** *Refer Review Notes on 'Schilling Test'*

***Shilling's test is typically done to determine the cause of cobalamine malabsorption (Vitamin B12 malabsorption) A diagnosis of Intrinsic factor deficiency can be established if radiolabelled cobalamine (Vitamin B12) appears in urine after administration of Intrinsic factor.***
*Schilling test is abnormal in conditions that affect cobalamine absorption including Intrinsic Factor Deficiency in Pernicious anemia, Exocrine Pancreatic Dysfunction in Chronic Pancreatitis, Bacterial overgrowth syndrome and Ileal dysfunction.*

**57. Answer is B (vitamin $B_{12}$ is Deficiency):** Harrison 18th/p 870 *Harrisons 16th/605,606; 17th/650; Harrison Appendix A for Reference values*

***Presence of anemia (Hb= 6gm%) Macrocytosis (MCV=104) and decreased vitamin B12 levels (B12=60 pg/ml) suggests a diagnosis of megaloblastic anemia due to vitamin B12 deficiency.***

Reference values from Harrison's Appendix A

| Parameter | Normal Values | Patient value | Inference |
|---|---|---|---|
| Hb | 13-18 g/dl | 6 gm/dl | Anemia |
| HCV | 79-93.3/L | 104 fL | Macrocytosis |
| Vitamin B12 | >250 pg/ml | 60 pg/ml | Vitamin B12 deficiency |
| Folic Acid | 5.4-18.0 ng/ml | 8 ng/ml | Normal folate levels |
| Iron | 30-160 µg/dl | 160 µg/dl | Normal |

***The patient in question, thus has a macrocytic anemia due to vitamin B12 deficiency.***

**58. Answer is A ($B_{12}$ Estimation) :** *Harrisons 16th/602, 603; Other references with text*

***Increased MCV*** *(normal MCV = 79- 93.3),* ***Anemia*** *(Normal Hb = 12 –16.2) and* ***characteristic oral manifestation (macroglossia and Atrophy of Papillae) suggest the diagnosis of vitamin $B_{12}$ deficiency. The next best step is to confirm the diagnosis by estimating vitamin $B_{12}$ levels.***

Oral Manifestations of vitamin $B_{12}$ deficiency : *Color Atlas of Oral Diseases by Scully & Welbury (1994)/109*

- Tongue may be large (***'Macroglossia'***$^{Q}$)-*Greenberg's Text-Atlas of Medicine/744*
- Tongue may be smooth due to **loss of papillae** *(Atrophic Glossitis)*$^{Q}$
- Tongue may show red patches on red lines on the ventrum *(Moeller's glossitis)*
- Tongue may be red and inflamed *(Sore tongue)*$^{Q}$
- *Angular cheilitis* may be associated
- *Oral ulcers* may be seen

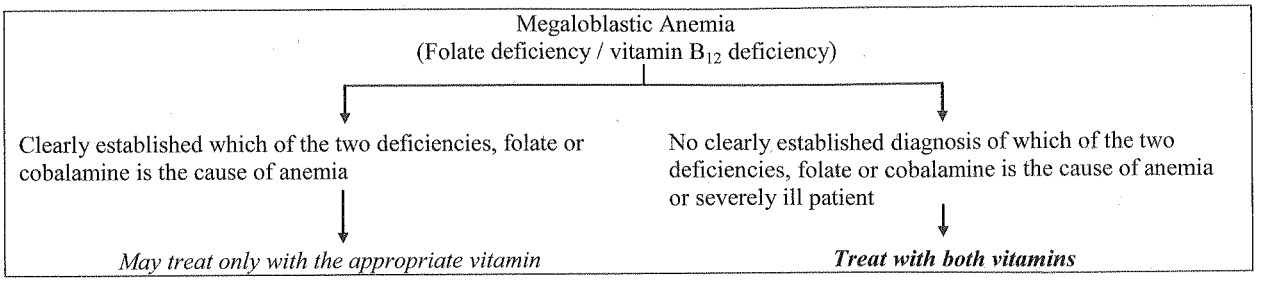
| Tongue in vitamin $B_{12}$ deficiency |
|---|
| *Macroglossia*$^{Q}$ |
| *Atrophic glossitis*$^{Q}$ |
| *Moeller's glossitis* |
| *Sore tongue*$^{Q}$ |
| *Beefy tounge*$^{Q}$ |

**59. Answer is A (Folic acid alone causes improvement in hematologic in symptoms but worsening of neurological symptoms):** *Harrison 18th/871; Robbins 7th/642, 643; Harrisons 17th/ 651*

*Megaloblastic anemia may be caused by a deficiency of vitamin B12 (cobalamine) or deficiency of folate. Unless it is clearly established, which of the two deficienceis / folate or cobalamine) is the cause anemia treatment should include administration of both folic acid and vitamin $B_{12}$.* ***If only folic acid is administered in a patient with megaloblastic anemia due to vitamin B12 deficiency, worsening of neurological symptoms (cobalamine neuropathy) is seen despite an improvement in the hematological symptoms (anemia)***

*'Although prompt hematologic response heralded by reticulocytosis follows the administration of folic acid, it should be cautioned that* ***the hematologic symptoms of a vitamin $B_{12}$ deficiency anemia also respond to folate therapy. However folate does not prevent and may even exacerbate the progression of neurological deficits typical of vitamin $B_{12}$ deficiency states'*** *– Robbins 6th/643*

*Before large doses of folic acid are given, cobalamine deficiency must be excluded and if present corrected, otherwise* ***cobalamine neuropathy may develop despite a response of the anemia of cobalamine deficiency to folate therapy*** *– Harrisons 17th/651*




## Hemolytic Anemias

### General Features

**60. Answer is C (Thalassemia):** *Hematology in Clinical Practice 4th/142, 143*

***Hemoglobinopathies including thalassemia cause extravascular hemolysis and not intravascular hemolysis.***

**Causes of intravascular hemolysis**

- Blood transfusion
  - ***ABO mismatched transfusion***
  - Infected blood
- *Thermal burns*
- *Snake bites*
- *Sepsis*
  - Bacterial / parasitic infections
  - Clostridial sepsis
  - Malaria
  - Bartonellosis
  - *Mycoplasma pneumoniae*
- *Mechanical heart valves*
- ***Paroxysmal hemoglobinuria***
  - PNH
  - PCH

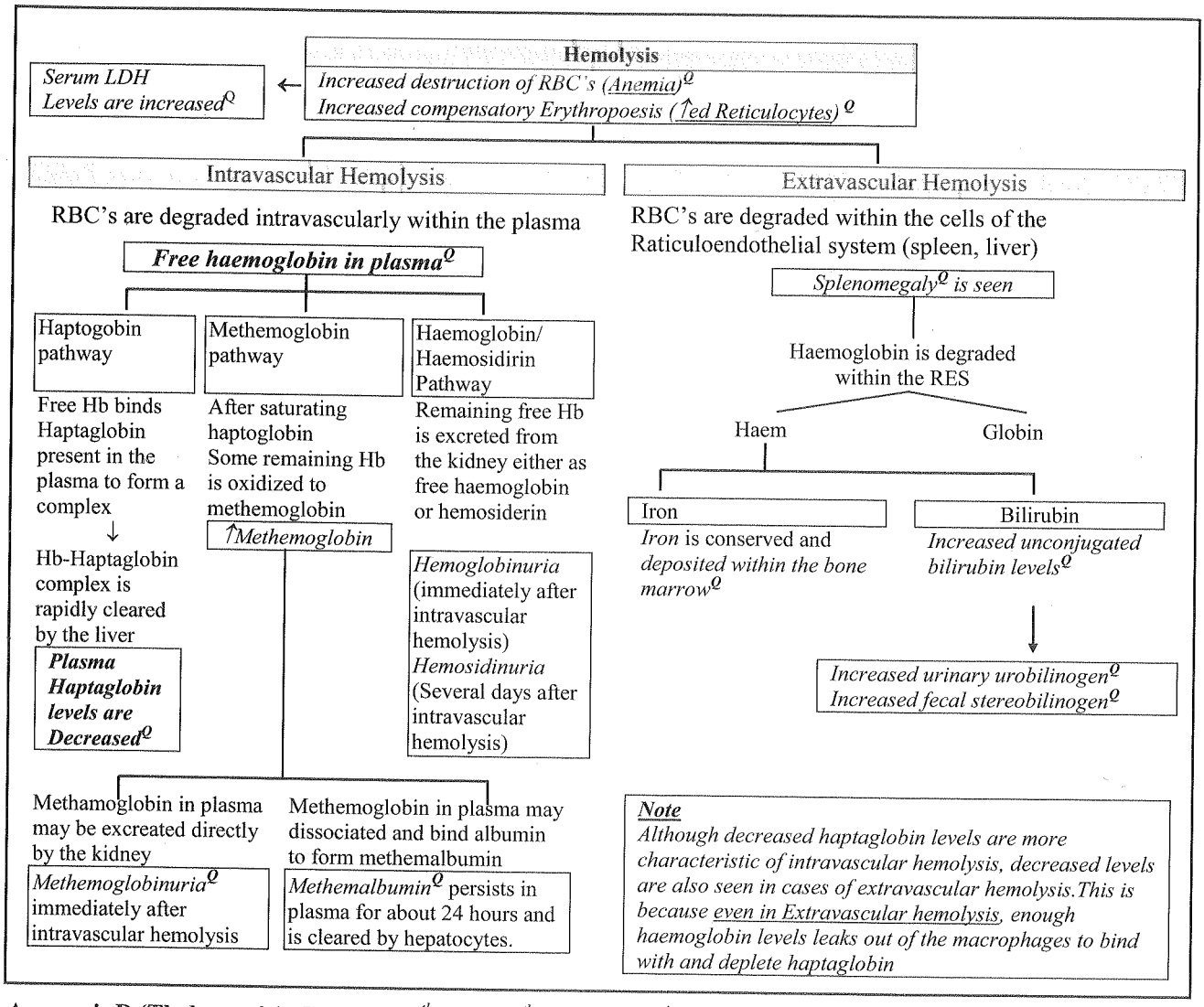
**Causes of extravascular hemolysis**

- Blood and viral infections
  - Malaria
  - *Mycoplasma pneumoiae*
  - Infectious mononucleosis
- Drug-induced hemolysis
  - G6PD/GSH deficiency
  - Autoimmune drug reactions
  - Strong oxidant drugs/chemicals
- Autoimmune hemolysis
  - Warm-reacting (IgG) AIHA
  - Cold-reacting (IgM) AIHA
- Hemoglobinopathies
  - ***Thalassemia***
- Membrane structural defect
  - Hereditary sperocytosis
  - Hereditary spherocytosis
  - Acanthocytosis
- Environmental disorders
  - Malignancy/DIC
  - TTP/HUS
  - Eclampsia or Preeclampsia

**61. Answer is D (Hereditary Spherocytosis):** *Hematology in clinical practice 4th/142,143; Refer previous questions*

***Hemoglobinuria is a feature of intravascular hemolysis. Amongst the options provided hereditary spherocytosis is a cause for extravascular hemolysis and is therefore not associated with hemoglobinuria.***

| Urine | Extravascular hemolysis | Intravascular hemolysis |
|---|---|---|
| Hemosiderin | 0 | + |
| Hemoglobin | 0 | + in severe cases |




**62. Answer is D (Thalassemia):** *Harrison 16th/ 607; 17th/ 652; API 8th/ 809; Chandrasoma Taylor 3rd/ 391*

***Haemoglobinuria is a feature of intravascular hemolysis. Amongst the options provided thalassemia is the only cause for extravascular hemolysis all others being causes for intravascular hemolysis.***

**Laboratory Evaluation of Haemolysis**

| | Extravascular | Intravascular |
|---|---|---|
| **Hematologic** | | |
| Routine blood film | Polychromatophilia | Polychromatophilia |
| Reticulocyte count | ↑ | ↑ |
| Bone marrow examination | Erythroid hyperplasia | Erythroid hyperplasia |
| **Plasma or serum** | | |
| Bilirubin | ↑ Unconjugated | ↑ Unconjugated |
| Haptoglobin | ↓ | Absent |
| Plasma hemoglobin | N - ↑ | ↑↑ |
| Lactate dehydrogenase | ↑ (Variable) | ↑↑ (Variable) |
| **Urine** | | |
| Bilirubin | 0 | 0 |
| Hemosiderin | 0 | + |
| Hemoglobin | 0 | + in severe cases |

**63. Answer is D (All of the above)**

*Decreased haptaglobin levels may occur in all cases of hemolysis.*

*Although decreased haptaglobin levels are more characteristic of intravascular hemolysis, decreased levels are also seen in cases of extravascular hemolysis.*

Heptaglobin levels and hemolysis *(Hematology for Student's by Mackinney (2003)/78,79*

- Normal plasma contains haptoglobin, an α2- globulin that can bind free haemolglobin
- During intravascular hemolysis as levels of free haemoglobin rise significantly, the levels of serum haptoglobin are observed to be very low or absent
- Even in Extravascular hemolysis, enough haemoglobin levels leaks out of the macrophages to bind with and deplete haptaglobin

Therefore

***A low serum haptaglobin concentration is a good test of hemolysis but is not specific for intravascular hemolysis.***

| Parameter | Extravascular hemolysis | Intravascular hemolysis |
|---|---|---|
| *Haptaglobin* | *Low* | *Very low/Absent* |

**64. Answer is A (Paroxsmal cold Haemoglobinuria):** *Hematology for Students by Mackinney (2003)/79*

***Chronic hemolysis due to paroxysmal cold Haemoglobinuria may be associated with iron deficiency***
*'In chronic extravascular hemolysis iron is tenaciously conserved. In chronic intravascular hemolysis large amounts of iron are lost in the urine as free haemoglobin, muthemoglobin and hemosiderin and the patient may become iron deficient'- Hematology for Students.*

***Amongst the options provided paroxysmal cold haemoglobinuria is a cause for intravascular hemolysis and hence the single best answer of choice***

*Thalassemia, Hereditary spherocytosis and G6-PD deficiency are all associated with extravascular hemolysis and are likely to present with iron overload and not iron deficiency*

**65. Answer is D (Bilirubin in urine):** Harrison 18th/p 873 *Harrision 17th/652*

***Presence of bilirubin in urine is not a feature of Hemolytic Anemias.***
*Presence of bilirubin in urine indicates the presence of conjugated bilirubin in the plasma. Hemolytic anemias are associated with unconjugated hyperbilirubinemia not conjugated hyperbilirubinemia.*

**Features of Hemolytic Anemia**

| **Features due to Increased Hemolysis (↓ed RBC life span)** | **Features due to Erythropoetic response of the bone marrow** |
|---|---|
| • *Hemoglobin : reduced*<br>• ↑ ***unconjugated bilirubin***<br>• ↑ *LDH*<br>• ↑ *AST*<br>• ↓ ***Haptoglobin***<br>• ↑ *Urobilinogen in urine (& stool)*<br>• ↑ *Stercobilinogen in stool*<br>• *Hemoglobinuria (intravascular hemolysis)* | • ↑ Reticulocytes (Reticulocytosis)<br>• ↑ MCV / ↑ MCH<br>(The increased number of reticulocytes is associated with an increased MCV)<br>• Macrocytes, Polychromasia & sometimes nucleated red cells in smear<br>• ***Erythroid Hyperplasia in marrow (Myeloid Erythroid Ratio is decreased)*** |

**66. Answer is D (Increased Haptoglobin):** Harrison 18th/p 873 *Harrison 17th/ 652; Harsh Mohan 4th/ 356*

***Hemoglobin binding proteins such as Haptoglobin are reduced or absent.*** *- Harsh Mohan 4th / 356*

**Characteristic features of Hemolytic Anemia:**

| **Increased red cell breakdown** | **Compensatory increase red cell production** |
|---|---|
| • Serum bilirubin is ↑ed *(unconjugated bilirubin ↑ed)Q*<br>• *Urine urobilinogen is ↑ed Q*<br>• *Fecal stercobilinogen is ↑ed Q*<br>• *Hemoglobinemia / Hemoglobinuria Q* | • *Reticulocyte **count is** ↑ed Q*<br>• *Routine blood film shows a variety of abnormal morphological types of red cells Q*<br>- *Schistocytes*<br>- ***Spherocytes** Q etc.* |

- *Methemoglobinemia* [Q]
- ***Hemosiderinuria*** [Q]
- ***Hemoglobin binding proteins*** [Q] ***such as Haptoglobin and Hemopexin are reduced or absent.*** [Q]
- *Plasma Lactic dehydrogenase* [Q] *(LDH) is* ↑[ed]
- *Bone narrow shows erythroid hyperplasia with raised iron stores.* [Q]
- *X Rays of bones show :*
  - ***Evidence*** *of expansion of marrow space, especially in tubular bones & in skull* [Q]
  - ***Bossing*** *of skull* [Q]

**67. Answer is D (Increased plasma Haptaglobin levels):** *Repeat*

***Hemolytic anemia are associated with decreased or absent levels of plasma haptaglobin.***
***Hyperbilirubinemia, Reticulocytosis and Hemoglobinuria are charachteristic features of hemolytic anemias.***

**68. Answer is A (Thrombocytopenia) :** *Repeat*

***Thrombocytopenia is not a feature of hemolytic anemia.***
*Decreased levels of serum haptaglobins, hemosidinuria and raised levels of indirect bilirubin are recognized feature of hemolytic anemias.*

**69. Answer is A (Tear drop cells are Burr cells) :** *Refer text below*

***Tear drop cells and Burr cells are not characteristic of hemolytic anemias.***
***Decreased levels of haptagobin, Reticulocytosis and haemoglobinuria are characteristic features of hemolytic anemia.***

**Burr cells and Tear Drop cells**- *'Pathology of Bone marrow and Blood cells (2004)'*

**Burr Cells** may be seen in cases of microangiopathic hemolytic anemia but the presence of burr cells alone is not characteristic of a hemolytic anemias.

**Burr cells (Echnocyte)**

*Burr cells are an acquired RBC membrane abnormality with short evenly spaced spicules.*
**They may be seen in**
- *Renal failure (Uremia) – Characteristic feature*
- Liver disease
- Burns
- Pyruvate kinase deficiency
- Gastric ulcers
- Cancer
- *Microangiopathic Hemolytic Anemias*

**Tear drop cells** are drop shaped cells characteristic of marrow fibrosis.
They are not a characteristic feature of hemolytic anemias.

**Tear Drop cells (Dacrocytes)**

*Tear Drop cells are drop/ tear shaped RBC's characteristically seen in conditions associated with marrow fibrosis or extramedullary hemotopaesis*
**They may be seen in**
- Myelofibrosis
- Myelodysplastic syndrome
- Sideroblastic anemia
- Metastatic marrow infiltration
- These may also be seen in thalassemia, pernicious anemia and iron deficiency anemia

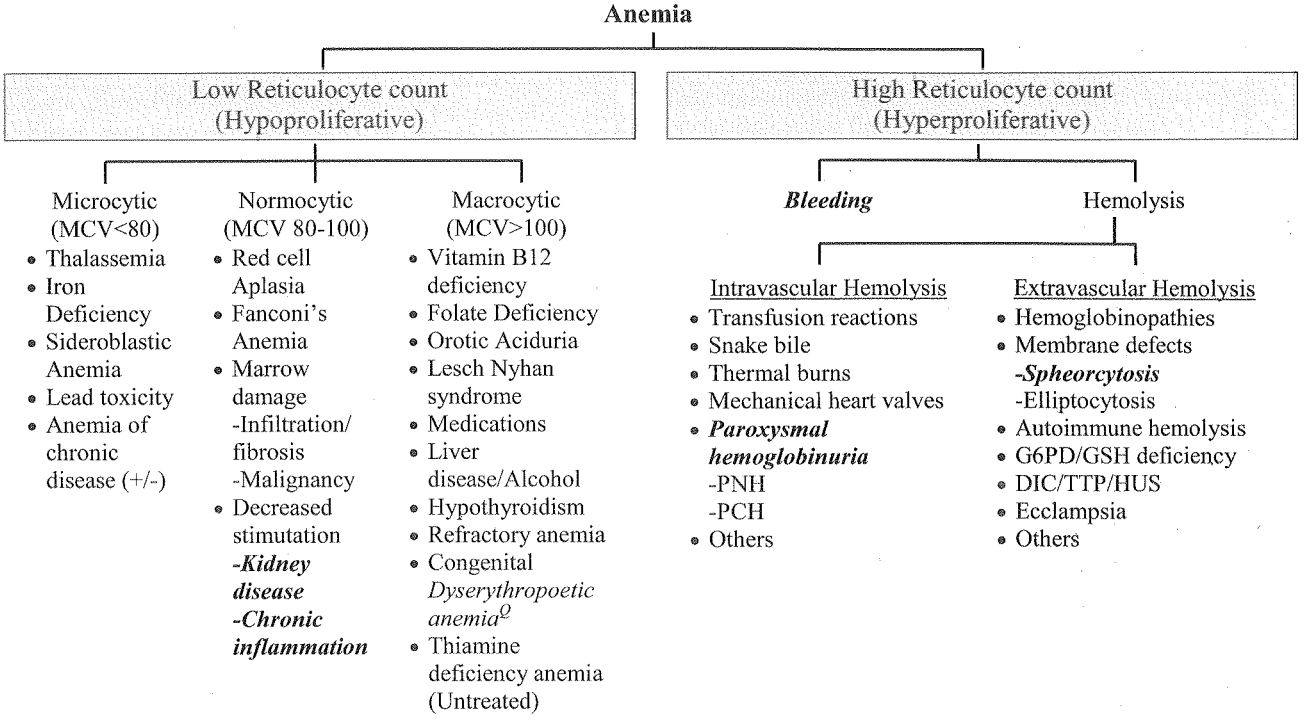
**Note**

Fragmented Erythrocytes seen in microangiopathic hemolytic anemia
- Helmet cells[Q]
- Burr cells[Q]
- Schistocytes[Q]

*Taken from Heptinstall's pathology of the kidney 6th/703.*

**70. Answer is D (Anemia of chronic Renal Failure):** *Refer previous questions*

***Anemias of chronic renal failure and chronic disease are associated with low or normal reticulocyte counts. Elevated reticulocyle count is a feature of hyperproliferative anemias including PNH, hereditary spherocytosis and anemia after blood loss.***




**71. Answer is both C and D (Nutritional Anemia and Congenital dyserythropoeitic anemia):** *Harrisons 16th/334; Refer previous question*

***Nutritional anemia is associated with normal/Low Retriculocyte count. Increased reticulocyte count (Reticulocytosis) is not a feature of nutritional anemias.***

**Nutritional Anemia**

*Anemia resulting from deficiency of important nutrients in diet is called Nutritional anemia. Nutritional anemia is most commonly seen secondary to deficiency of Iron (Iron deficiency anemia) and vitamin B12 and Folic acid (Megaloblastic anemia). Both iron deficiency anemia and megaloblastic anemia are associated with low reticulocyte count.*

**Congenital Dyserythropoetic Anemia** (CDA's) (Essential Hematology by Moss 4th/97)

Congenital dyserythropoetic anemias are a group of hereditary refractory anemias characterized by ineffective erythropoesis.

The reticulocyte count in these disorders in characteristically low (to normal for the degree of anemia).

**Paroxysmal Nocturnal haemoglobinuria (PNH)**

Paroxysmal Nocturnal Haemoglobinuria is associated with Intravascular hemolysis and is a known cause for elevated Reticulocyte count.

**Hemolysis**

Both intravascular and extravascular hemolysis are characterized by elevated reticulocyte counts

**Reticulocyte count**

**Low/Normal Reticulocyte count (Reticulocyte production index <2.5)**

**Hypoproliferative (Normocytic Normochromic)**
- Marrow damage
  - Aplasia
  - Infiltration/fibrosis
- Iron deficiency
- Decreased stimulation
  - Inflammation (chronic disease)
  - Renal disease
  - Metabolic defect

**Maturation disorder (Microcytic or Macrocytic)**

**Cytoplasmic defect**
- Iron deficiency (B+I)
- Thalassemia
- Sideroblastic Anemia

**Nuclear Defect**
- Folate deficiency
- Vitamin B12 deficiency
- Drug toxity
- Refractory Anemia ***(Congenital Dyserythropoetic anemia)***

Nutritional Anemia *are anemias secondary to deficiency of nutrients such as iron, vitamin B12 and folic acid and cause anemia with low / normal reticulocyte count.*

**High Reticulocyte count Reticulcyte production index >2.5**

**Haemorrhage /Hemolysis**
- Blood loss
- Intravascular hemolysis
  - ***PNH***
  - PCH
  - Snake bite
  - Transfusion mismatch
  - Thermal burns etc
- **Extravascular hemolysis**
  - Hemoglobinopathy
  - Autoimmune hemolysis
  - G6PD /GSH deficiency
  - Membrane defect
  - Hereditary spherocrtosis
  - Hereditary elliptocytosis
- **Miscellaneous**
  Fragmentation Hemolysis.

**72. Answer is D (Anemia in C.R.F.):** Harrison 18th/p 850, 885, 886 *API 6th/ 856, API 7th/ 923; Harrison 17th/ 633, 634, 662; CMDT 2008/430*

*Anemia of chronic disease is associated with a normal / low Reticulocyte count.*

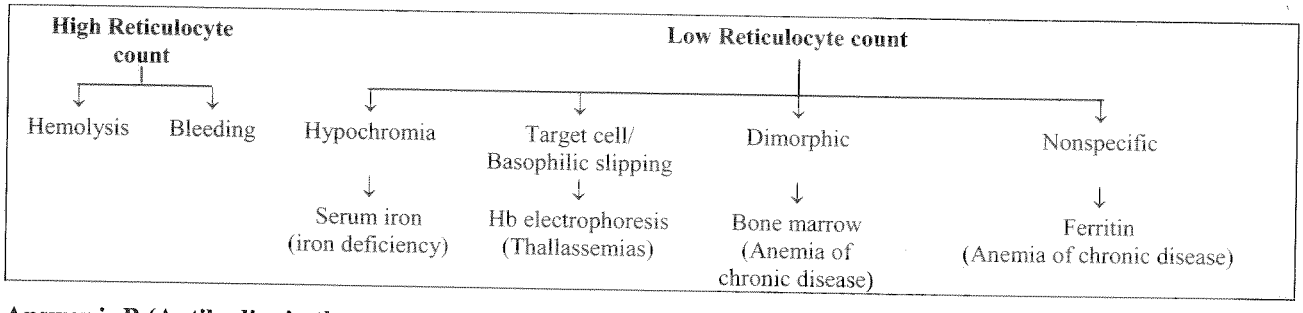
***Reticulocytes are young red cells with presence of nuclear remnants in the cytoplasm. Their number gives an estimate of the adequacy of marrow response to anaemia.***

**Reticulocyte count (Normal is 0.5 to 1.5% of all red cells):**

| High Reticulocyte Count | Low Reticulocyte Count |
|---|---|
| 1. Haemolysis from any cause eg. Haemolytic anemias including hereditary Spherocytosis & PNH. | 1. Aplastic anemia |
| 2. Bleeding (Blood loss) | 2. Nutritional deficiency anemia. |

*Note: Reticulocytosis occurs in nutritional anemias as soon as treatment is started.*

**Diagnostic approach based on assessment of reticulocyte count in patients with normal or low MCV**

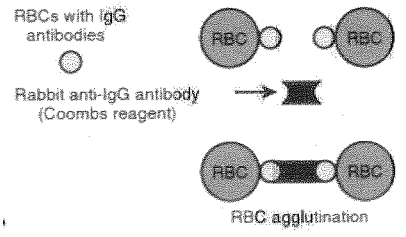


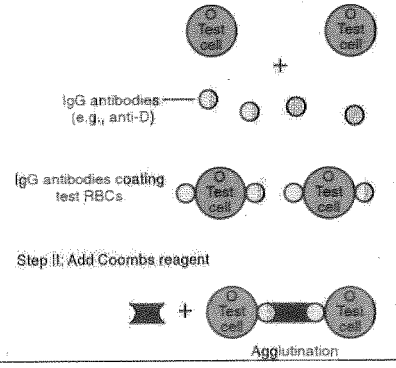

**73. Answer is B (Antibodies in the serum):** *Rapid Review Pathology: with STUDENT CONSULT (Elsevier Health Sciences, 2013)/313; Essentials of Immunology and Serology (Cengage Learning, 2002)/219; Harrison's 18th/881*

***Indirect Coomb's test detects IgG antibodies in the serum (e.g. Anti-D Antibodies). Direct Coomb's test detects IgG Antibodies (or complements) attached to the surface of RBCs.***

| **Direct Antihuman Globulin Test** *(DAT; Coomb's; Direct Coomb's)* | ***Detects RBCs sensitized with IgG or Complements(C3B or C3d)*** *Detects IgG Antibodies (or complements) attached to the surface of RBCs.* |
|---|---|

| **Indirect Antihuman Globulin Test** *(Indirect Coomb's)* | ***Detects Antibodies in the Serum*** |
|---|---|

| Direct Coomb's Test |
|---|
| In the Direct Coomb's test, red blood cells (RBCs ) sensitized with IgG antibodies (or C3b, C3d) are agglutinated when Coomb's reagent (Rabbit Anti-IgG antibody) is added to the test tube |
|   |

| Indirect Coomb's Test |
|---|
| In the Indirect Coomb's test IgG antibodies (e.g. Anti-D) in the serum must first bind to blood group Type O Test RBCs added to the test tube. Addition of Coombs Reagent, then causes the sensitized Type O Test RBCs to agglutinate, indicating that IgG antibodies are present in the serum |
|   |

**74. Answer is A (Antibodies attached to RBC Surface):** *Rapid Review Pathology: with STUDENT CONSULT (Elsevier Health Sciences, 2013)/313; Essentials of Immunology and Serology(Cengage Learning, 2002)/219; Harrison's 18th/881*

***Direct Coomb's test detects IgG Antibodies (or complements) attached to the surface of RBCs. Indirect Coomb's test detects IgG antibodies in the serum (e.g. Anti-D Antibodies).***

## Hereditary Spherocytosis

**75. Answer is C (Glycophorin–C):** *Harrisons 16th/609*

***Hereditary spherocytosis is not associated with molecular abnormality in Glycophorin – C.***

**Molecular Abnormalities in Hereditary Spherocytosis**

Molecular abnormalities in Hereditary spherocytosis primarily involve the proteins responsible for tethering the lipid bilayer to the underlying cytoskeletal network.

| **Proteins that may be defective in Hereditary sphenocytosis** | |
|---|---|
| • ***Ankyrin:*** *(Most common defect)♀* | : (Defective in about 50% of cases) |
| • ***Protein 3: (Anion transport channel)*** | : (Defective in about 25% of cases) |
| • ***Spectrin*** : (Spectrin or α spectrin) | : (Defective in most of remaining 25% of cases) |
| • ***Palladin*** : *(Protein 4.2)♀* | : (Rare defect, but may cause H. S) |
| ***Protein Defects causing H.S*** | : ***Ankyrin > Protein 3 ≥ Spectrin > Palladin*** |

**76. Answer is C (MCV ↑ed):** Harrison 18th/p 875, 876 *Harrison 17th/ 654, 655;*

***Mean corpuscular volume of RBC is decreased in patients with hereditary spherocytosis.***

**Hereditary spherocytosis** is characterised by defect in one of the proteins in the cytoskeleton of Red cell membrane, leading to loss of membrane, and hence ***decreased ratio of surface area to volume*** and consequently spherocytosis.

**Characteristic Laboratory abnormalities**

- *The mean corpuscular volume (MCV) : is decreased* ♀
- *The mean corpuscular Hb. concentration (MCHC) : is increased* ♀
- *Osmotic fragility is : increased* ♀

**Remember the following also :**

| | | |
|---|---|---|
| • *Hereditary spherocytosis is inherited as* | : | *Autosomal dominant* ♀ |
| • *Most common membrane defect is that of* | : | *Ankyrin* ♀ |
| • *One characteristic clinical presentation is* | : | *Striking splenomegaly* ♀ *(anemia, splenomegaly, jaundice)* |
| • *Treatment of choice is* | : | *Splenectomy* ♀ |

**77. Answer is A (Direct Coomb's Positive):**

***Hereditary Spherocytosis is a Coomb's Negative Haemolytic Anaemia.***

Coomb's test is important to distinguish Hereditary Spherocytosis from Autoimmune haemolysis which is another common cause of Spherocytosis. Hereditary Spherocytosis is a coomb's negative haemolytic anemia (non-immune mediated) characterized clinically by anaemia, jaundice, splenomegaly and pigment gall stones. Typical Laboratory findings include spherocytosis (abundant spherocytes on peripheral smear) and increased osmotic fragility. There is no definitive treatment to correct the primary defect in the membrane cytoskeletal structure. Splenectomy remains the treatment of choice for severe cases of Hereditary Spherocytosis (since Spleen is the primary site of destruction of red blood cells and transit through the splenic circulation makes them more spherocytic thereby accelerating their death.)

**78. Answer is C (Most common mode of inheritance is Autosomal Recessive):** *Harrison 18th/ 875*

*Presence of numerous Spherocytes in the blood together with a family history of Splenectomy suggests a possible diagnosis of Hereditary Spherocytosis.* ***The most common mode of inheritance in Hereditary Spherocytosis is Autosomal Dominant (Classical Inheritance).*** *Autosomal Recessive inheritance however may also be seen but is less common.*

**79. Answer is B (Aplastic Crisis):** *Oxford Textbook of Medicine 4TH/712; Wintrobe's Clinical Hematology 13TH/714*

***Parvovirus B19 selectively infects erythroid precursors and is the most common aetiological agent that induces Aplastic Crisis in patients with Hereditary Spherocytosis (and other Hemolytic disorders).***

**Parvovirus B19 and Aplastic Crisis**

- Parvovirus B19 selectively infects erythroid precursors and inhibits their growth
- Erythropoietic arrest leads to a sudden decrease in hemoglobin concentration and reticulocytopenia (Aplastic Crisis)
- Aplastic/hypoplastic crises resulting from parvovirus B19 infection may occur in patients with hereditary spherocytosis (H.S), as in individuals with other chronic homolytic disorders.
- Parvovirus infection may be the first manifestation of HS
- Recovery typically occurs within 7 to 10 days and is heralded by reticulocytosis and thrombocytosis.
- Infection with parvovirus is a particular threat to susceptible pregnant women, because it can infect the fetus, leading to severe anemia, hydrops fetalis, and fetal death.

**80. Answer is A (Parvovirus):** *Robbins 7th/627*

***Aplastic crisis is usually triggered by an acute parvovirus infection.***

**81. Answer is D (Aplastic Crisis are Common):** *Oxford Textbook of Medicine 4TH/712; Wintrobe's Clinical Hematology 13TH/714*

***Aplastic Crisis are a rare / uncommon complication of Hereditary Spherocytosis*** *typically caused by virally induced bone marrow suppression.*

*The most common aetiological agent that induces Aplastic Crisis in patients with Hereditary Spherocytosis is Parvovirus B19.*

**Hereditary Spherocytosis usually has autosomal dominant inheritance caused by mutations in genes for proteins such as spectrin, ankrin or band 3**

The genes responsible for HS include ankyrin, β spectrin, band-3-protein, α-spectrin, and protein 4.2. In approximately two-thirds to three-quarter of HS patients, ***inheritance is autosomal dominant.*** In the remaining patients, inheritance is non-dominant due to autosomal recessive inheritance or a de novo mutation.

**In patients with Hereditary Spherocytosis Red blood cells are destroyed in the spleen**

The spleen plays a critical role in the pathoblology of HS, as destruction of spherocytes in the spleen is the primary cause of hemolysls in HS patients.

**Aplastic Crisis is an Uncommon Complication**

Aplastic crises following virally induced bone marrow suppression ***are uncommon***, but may result in severe anaemia with serious complications including congestive heart failure or even death. *The most common aetiological agent in these cases is parvovirus BI9.* Parvovirus selectively infects erythropoietic progenitor cells and inhibits their growth.

**82. Answer is C (Hereditary spherocytosis):** *Harrison 18th/p 875; 'A manual of Laboratory and Diagnostic Tests' 8th/116, 117; Harrison 17th/654*

***Hereditary spherocytosis is characteristically associated with an increased osmotic fragility.***

**Osmotic Fragility**

Osmotic fragility of red cells is defined as the ease with which red cells are ruptured (hemolysed) when they are exposed to hypotonic solution.
Osmotic fragility test assesses the integrity of the membrane of red cells.

| Increased Osmotic Fragility | Decreased Osmotic Fragility |
|---|---|
| Cells which have a lower surface to volume ratio such as spherocytes from any cause have increased osmotic fragility<br>Conditions<br>• ***Hereditary spherocytosis (HS)***<br>• Autoimmune Hemolytic Anemias (AIHA)<br>• Hemolytic Disease of new born<br>• Malaria<br>• Severe pyruvate kinase deficiency<br>• Other conditions in which spherocytes are found in the blood | Cells which have a high surface to volume ratio such as thin/hypochromic/target cells have decreased osmotic fragility.<br>• ***Thalassemia*** *(other hemoglobinopathies eg. HbC, HbS)*<br>• *Iron deficiency anemia*<br>• ***Sickle cell anemia***<br>• *Post splenectomy*<br>• *Reticulocytosis*<br>• *Other conditions in which thin/target cells are found in the blood.* |

**83. Answer is B and D (Sickle cell ds and Thalassemia):** *'Practical Physiology by Pal and Pravati 2nd/104; Manual of Laboratory and Diagnostic Tests 8th/116, 117; Refer previous question*

***Hemoglobinopathies with increased target cells such as sickle cell disease, Thalassemias, HbC disease etc are associated with decreased osmotic fragility.***

*Hereditary spherocytosis and Autoimmune Hemolytic Anemias are characteristically associated with an increased osmotic fragility.*

**84. Answer is B (Hereditary spherocytosis):** *Harrison 18th/876; Harrison 15th/ 682, 16th/ 608; 17th/ 654*

***Splenectomy is curative in hereditary spherocytosis.***

*Splenectomy is carried out in all symptomatic patients Q because of the potential for gall stones and stones and episodes of bone marrow hyperplasia or hemolytic crisis Q*

- It reliably corrects the anemia and RBC survival often becomes normal or nearly so.
- The operative risk is low.

**Remember**

*Splenectomy is not carried out in young children ♀ (preferably postponed until age 4) in order to minimize the risk of severe infections ♀ with gram positive encapsulated organisms.*

**85. Answer is D (Prolonged Anti-pneumococcal Antibiotic Prophylaxis must be given after Splenectomy):** *Harrison 18th/ 876*

***Anti-pneumococcal vaccination before Splenectomy is imperative while anti-pneumococcal prophylaxis Post-Splenectomy is controversial.***

| Guidelines for Splenectomy in patients with Hereditary Spherocytosis |
|---|
| • Avoid Splenectomy in mild cases<br>• Delay Splenectomy until at least 4 years of age after the risk of severe sepsis has peaked<br>• Anti-pneumococcal vaccination before Splenectomy is imperative while anti-pneumococcal prophylaxis Post-Splenectomy is controversial |

## G6 PD Deficiency

**86. Answer is D (X-linked disorder not seen in females): Multiple references**

*G6 PD is an X linked Recessive Disorder that may affect both Males and Females.*

**G6 PD is an X linked Recessive Disorder that may affects both Males and Heterozygous Females**

*The (G6PD) gene is located on the X chromosome and shows a characteristic X-linked pattern.*

| Men can be | Women can be |
|---|---|
| • Normal hemizygous (have the normal allele) or<br>• Deficient hemizygotes (have a variant allele). | • Normal homozygous (both alleles normal),<br>• Heterozygotes (one normal allele and one abnormal allele)<br>• Deficient homozygotes (both alleles abnormal), or |

***The level of G6PD enzyme in female heterozygotes lies between normal and deficient due to the random inactivation of one of the X chromosomes in each cell (lyonization).***

According to the Lyon hypothesis (the validity of which is strongly supported by G-6-PD genetics), only one X chromosome is active in any somatic cell. Thus, individual red cells of females contain only one G-6-PD type and a given red cell in heterozygous-deficient females is either normal or deficient. Red cell stains confirm the presence of two cell populations. Mean enzyme activity in deficient females may be normal or moderately reduced (the usual pattern), or grossly decreased, depending on the degree of "lyonization". Deficient cells in females are as susceptible to oxidant injury as deficient cells in males. ***The severity of hemolysis is less, however, because fewer vulnerable cells are present.***

**G6PD deficiency affects the pentose phosphate pathway**

**G-6-PD is an enzyme that catalyses the first reaction in the *pentose phosphate pathway***, to produce NADPH (Reducing power), which is an important antioxidant to deal with oxidative stress. Red Cells lack any other source of NADPH and are solely dependent on the pentose phosphate pathway, so G-6-PD deficiency leaves these cells with no defence against oxidative stress.

In most cells the purpose of the pentose phosphate pathway is essential for the generation of Ribose and its incorporation into RNA. ***In the red cell the purpose of the pentose phosphate pathway is only to generate reducing power in the form of NADPH.*** Under normal circumstances *about 10 percent of glucose is metabolized by the pentose phosphate pathway but under conditions of oxidative stress the flux through the pentose phosphate pathway is greatly increased*

**G6 PD Deficiency can be precipitated by Broad Beans**

*Precipitating factors for hemolysis in G6PD Deficiency typically include Drugs, Infections and consumption of Flava Beans or Broad Beans (Favism)*

| Precipitating factors for Hemolysis in G6PD Deficiency |
|---|
| • *Drugs (Certain Drugs),* |
| • *Infections* |
| • *Consumption of Flava Beans or Broad Beans (Favism)* |

**Neonatal Jaundice is one of its typical presentations**

*'The vast majority of patients with G6PD Deficiency remain asymptomatic throughout their life time, however all of them have an increased risk of developing neonatal jaundice (NNJ) and a risk of developing acute haemolytic anemia when challenged by a number of oxidative agents. NNJ related to G6PD Deficiency is rarely present at birth ; peak incidence of clinical onset is between day 2 and day 3 and in most cases anemia is not severe' – Harrison 17th/657*

| **Typical Clinical Manifestations of G6PD Deficiency** |
|---|
| • *Acute Hemolytic Anemia (Drug Induced ; Infection Induced)* |
| • *Favism (Exposure to Fava Beans – Vicia Fava or Broad Beans)* |
| • *Neonatal Jaundice* |
| • *Chronic/Congenital Non Spherocytic Hemolytic Anemia (CNSHA)* |

87. **Answer is C (Contradicts Lyon Hypothesis) :** *Multiple references*

***Validity of Lyon Hypothesis is strongly supported by genetics of G6PD Deficiency***
*G6 PD is an X linked Recessive Disorder that may affects both Males and Females. Because G6PD Deficiency is inherited as an X-Linked (Recessive) disorder G6PD deficiency is more common in males. Heterozygous Females may also be affected depending on the extent of Lyonization (Inactivation of one X Chromosome), but the overall degree of hemolysis in heterozygous females is less (Less severe than males who are Hemizygous).*

**Validity of Lyon Hypothesis is strongly supported by genetics of G6PD Deficiency**

The Lyon hypothesis maintains that one of two X chromosome in each cell of the female embryo is inactivated and remains inactive throughout subsequent cell divisions for the duration of life. *In fact, it was studies by Beutler on females with G6PD deficiency which were used in proof of the Lyon hypothesis*

**G6 PD follows an X linked Inheritance**

***The G6PD gene is located on the X chromosome and shows a characteristic X-linked pattern.*** *G6 PD is an X linked Recessive Disorder*

**Heterozygous females may be affected but severity of hemolysis is generally less**

Heterozygous females are often susceptible to oxidative stress because of the effects of X-inactivation and marked lyonization in leaving a significant population of deficient red cells. ***The level of G6PD enzyme in female heterozygotes lies between normal and deficient*** due to the random inactivation of one of the X chromosomes in each cell (lyonization). Mean enzyme activity in deficient females may be normal or ***moderately reduced (the usual pattern),*** or grossly decreased, depending on the degree of "lyonization". ***The overall severity of hemolysis in females is however less, because the total number of vulnerable cells (red cells with the inactivated normal allele) are less.***

**Inheritance in Men with one abnormal allele**
Men have a single X – Chromosome and hence all men with a variant allele are deficient **hemi**zygotes. All individual red cells in men are deficient.

**Inheritance in Females with one abnormal allele**
- Women have two X-chromosomes and hence women with one normal allele and one abnormal allele are Heterozgotes.

  According to the Lyon hypothesis (the validity of which is strongly supported by G-6-PD genetics), only one X chromosome is active in any somatic cell.

- Heterozygous females therefore contain two cell populations of red cells
  -*Normal* where the X chromosome with the deficient allele is inactivated
  -*Deficient* where the X chromosome of the normal allele is inactivated
- A given red cell in heterozygous-deficient females is either normal or deficient.
- Deficient cells in females are as susceptible to oxidant injury as deficient cells in males.
- ***The overall severity of hemolysis in females is however less, because the total number of vulnerable cells (red cells with the inactivated normal allele) are less.***

**88. Answer is A (Class I) :** *Multiple references*

***Chronic Non Spherocytic Anemia is associated with Severe G6PD Deficiency and is exclusively classified as Class I of the WHO Classification.***

*Favism is mainly associated with Class II (Though Not Exclusively).*
*Neonatal Jaundice has been described with Class I, II and III , though it is most commonly seen in Class II and III*

**Clinical features**

- There are four main syndromes associated with G6PD deficiency.

| Four main syndromes associated with G6PD deficiency. |
|---|
| • *Acute Hemolytic Anemia (Drug Induced ; Infection Induced)* |
| • *Favism (Exposure to Fava Beans – Vicia Fava or Broad Beans)* |
| • *Neonatal Jaundice* |
| • *Chronic/Congenital Non Spherocytic Hemolytic Anemia (CNSHA)* |

- In all four, haemolysis is aggravated or promoted by exposure to oxidativc stress through infection or ingestion of oxidative foods or drugs, but the clinical presentations differ.

- The different variants of G6PD have been divided into classes by the World Health Organization, based on clinical symptoms and amount of enzyme activity.

| | | |
|---|---|---|
| Class I | Includes rare variants with severe enzyme deficiency | ***Gives rise to chronic nonspherocytic hemolytic anemia (CNSHA).*** |
| Class II | Includes variants with severe deficiency (less than 10% enzyme activity) and No CNSHA; | Can lead to severe, episodic acute hemolytic anemia associated with infections and certain drugs and foods.<br>Variant in this class include<br>G6PD-Mediterranean |
| Class III | Includes variants with moderate deficiency (10% to 60% enzyme activity) and No CNSHA | Can lead to episodic acute hemolytic anemia associated with infections and certain drugs, but it is usually self-limited.<br>Variants in this class include:<br>G6PD-A (found in approximately 10% of African American men)<br>G6PD-Canton (prevalent in Southeast Asia) |

| Class IV (Not clinically relevant) | Class V (Not clinically relevant) |
|---|---|
| Includes variants with normal enzyme activity (60% to 150%) associated with no hemolysis. | Includes variants with increased enzyme activity (greater than 150%), but this category is not clinically relevant. |

**89. Answer is C (Pyrimethamine):** Harrison 18th/p 879 *Harrisons 17th /657*

***Primaquine** is associated with definite risk, **Chloroquine** is associated with possible risk and **Quinine** is associated with doubtfull risk of inducing clinical hemolysis in persons with G6PD deficiency.*

***Pyrimethamine* is not mentioned in the list of drugs that carry risk of hemolysis and is the single best answer of exclusion**

**Drugs that carry risk of clinical hemolysis in persons with G6PD deficiency:** *(Harrison)*

| Agent | Definite risk | Possible risk | Doubtful risk |
|---|---|---|---|
| Antimalarials | **Primaquine**<br>Dapsone/Chlorproguanil | **Chloroquine** | **Quinine** |
| Sulphonamides/Sulphones | Sulphametoxazole<br>Others<br>Dapsone | Sulfasalazine<br>Sulfadimidine | Sulfisoxazole<br>Sulfadiazine |
| Antibacterial/Antibiotics | Cotrimoxazole<br>Nalidixic acid<br>Nitrofurantoin<br>Niridazole | Ciprofloxacin<br>Norfloxacin | Chloramphenicol<br>p-Aminosalicylic acid |
| Antipyretic/analgesics | Acetanilide<br>Phenazopyridine (Pyridium) | Acetylsalicylic acid high dose (>3 g/d) | Acetylsalicylic acid <3 g/d<br>Acetaminophen<br>Phenacetin |
| Others | Napthalene<br>Methylene blue | Vitamin K analogues<br>Ascorbic acid >1 g<br>Rasburicase | Doxorubicin<br>Probenecid |

**90. Answer is A (Oestrogen):** Harrison 18th/p 879 *Harrison 17th/657*

***Oestrogen is not included in the list of drugs that carry rick of hemolysis in patients with G-6 PD deficiency.***

***Primaquine* and *Nitrofurantoin* are associated with definite risk while *salicylates* are associated with a possible risk of hemolysis in G6 PD deficient patients.**

**91. Answer is A (G-6 PD deficiency):** Harrison 18th/p 878, 879 *Harrison 15th/ 685, Harrison 16th/ 611; Harrison 17th/ 657 (Add table 101.5)*

Erythrocytes are vulnerable to oxidative injuries by a variety of endogenous and exogenous oxidants. Glucose 6-PD, prevents such oxidative damage by maintaining the supply of reduced glutathione which inactivates such oxidants. In the absence of G 6 PD therefore patient may experience an acute hemolytic crisis within hours of exposure to oxidants stress.

**Drugs causing hemolysis in subjects deficient in G6PD are :**

1. *Antimalarials : Primaquine*
2. Sulfonamides : Cotrimoxazole
3. *Nitrofurantoin, Nalidixic acid* Q
4. *Analgesics : Aspirin, Phenocetin* Q
5. *Antiarrhythmics : Procanamide, Quinidine* Q
6. *Dapsone* Q
7. *Vit C, Vit K, Probenecid, Furazolidone* Q

## Hemoglobinopathies: Sickle Cell Anemia

**92. Answer is B (Replacement of glutamate by valine in beta chain of Hb):** *Harrison 18th/p 854; 17th/637 639 Robbins 7th/628*

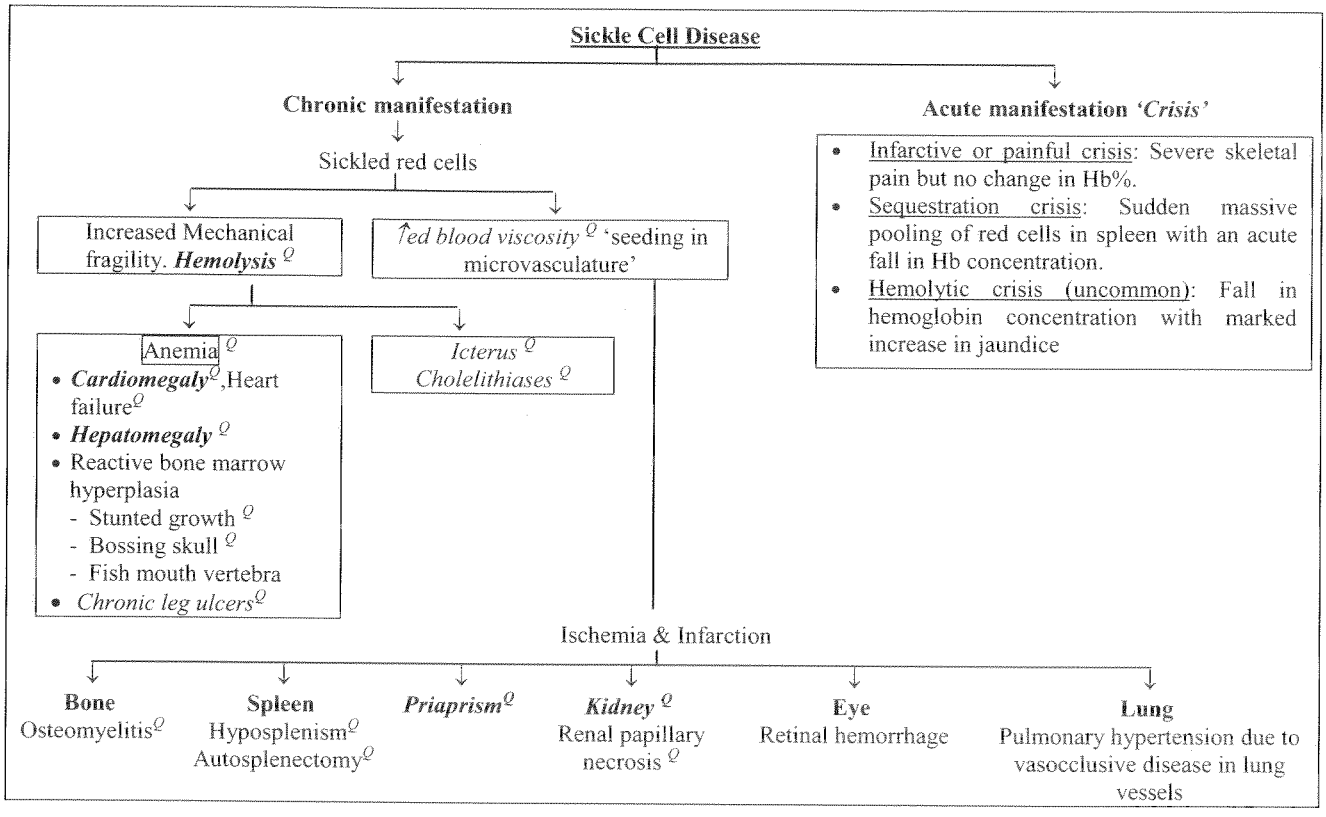
***The sickle cell anemia is caused by a mutation in the beta globin gene that changes the sixth amino acid from glutamic acid to valine in the beta chain of HbA ($\alpha_2\beta_2$).***

| Designation | Mutation |
|---|---|
| HbS (Sickle) ($\beta^{6Glu} \rightarrow$ Val) | Replacement of Glutamate by Valine at position 6 beta chain of HbA |
| HbC ($\beta^{6Glu} \rightarrow$ Lys) | Replacement of Glutamate by Lysine at position 6 on beta chain of HbA |
| HbE ($\beta^{26Glu} \rightarrow$Lys) | Replacement of Glutamate by Lysine at position 26 on beta chain of HbA |

**93. Answer is D (Splenomegaly):** Harrison 18th/p 855 *Harrison 17th/ 638; Read text*

***"Sickle cell anemia is characterized by Hyposplenism /Autosplenectomy (not Splenomegaly)".***

***Repeated episodes of splenic infarction cause the spleen to be reduced to small calcified remnant – a phenomenon that has been termed as 'Autosplenectomy'."***




**94. Answer is C (Leukopenia):** Harrison 18th/p 855 *Harrison 17th/ 637, 638;CMDT to be added; Read reference below*

***Sickle cell anemia is associated with granulocytosis (leukocytosis) and not leukopenia.***

- The ***white blood cell count is characteristically elevated*** to 12,000-15,000/μL. – *CMDT 2003 / 481.*
- Chronic acute or subacute pulmonary crisis (pulmonary vasocclusive disease) lead to pulmonary hypertension and cor pulmonale – *Harrisons 16th/ 596*
- The heart is enlarged with a hyperdynamic precordium and systolic murmurs – *CMDT 2003 / 481*
- Reactive hyperplasia of bone marrow with associated widening of medullary cavities produces a characteristic 'biconcave vertebra' i.e. fish mouth vertebra.

**95. Answer is D (Patient presents early in life before 6 months of age):** Harrison 18th/p 855, 856 *Harrison 17th edn /637,638; Nelson 17th edn 1624*

- ***Affected newborn seldom exhibit clinical features of sickle cell disease. Anemia develops over the first 2-4 months paralelling the replacement of much of the fetal haemoglobin by HbS. Clinical manifestations are uncommon before 5-6 months of age'*** – *Nelson 17th / 1624*
- The most important factor which affects the rate and degree of sickling (polymerization) ***is amount of HbS*** and its interaction with other Haemoglobin chains – *Robbins*

**Factors favouring polymerization:** Q

1. **Hypoxia** Q : (2,3 diphosphoglycerate increases polymerization Q)
2. **Acidosis** Q : decreased pH enhances polymerization Q
3. **Haemoglobin** concentration Q: Higher concentration leads to increased polymerization Q
4. **Combination of HbS with other haemoglobins**: This depends on the extent of homology with other haemoglobins. Descending order of ability to copolymerization are HbS, C, D, O, Arab, A, J & F ***(Least with HbF)***

- Acute splenic sequestration has a peak incidence between 6 months and 3 years and can be rapid in onset and lead to death. ***The most common cause of mortality is sepsis*** and acute chest syndrome'-*Nelson 17th/ 1626*
- ***Chronic transfusion therapy*** (repeated blood transfusions) has been used to decrease the frequency of crisis and may be useful in some severely affected patients - *Harrison*

**96. Answer is A (Mutation in α chain):** Harrison 18th/p 855, 854 *Harrison 17th/637, 638; Robbin's 7th/629*

***Sickle cell disease is caused by a mutation in the β globin gene that codes for β chain and not by a mutation in the 'α-chain'.***

**Sickle cell disease is caused by a mutation in the β gene** (H17th/637)

- The sickle cell syndrome is caused by a mutation in the β chain from glutamic acid to valine ($\alpha 2\beta 2^{6Glu\text{-}val}$)

**Severity of sickle cell disease may be decreased by HbF** (Robbins/Internal Medicine)

- Fetal Hemoglobin (HbF) inhibits the polymerization of HbS (Robbins)
- By inhibiting polymerization of HbS, HbF diminishes the severity of sickle cell disease – Internal Medicne 5th/659
  Patients with higher HbF levels have fewer pain episodes and longer survival – Internal Medicine 5th/659
- 'Through uncertain mechanisms, Hydroxyurea causes an increase in the levels of HbF in red cells. This may in part, be responsible for the mechanism of action of Hydroxyurea in sickle cell disease.
- Efforts are currently being directed towards gene therapy that would increase the production of HbF.

**Venoocclusive crisis is a cause of morbidity** (H 17th/638; Robbins 7th/632)

*Venoocclusive disease in sickle cell syndrome is a major cause of morbidity as it leads to repeated episodes of painful ischemia – painful crisis*

*'Some patients are crippled by repeated vaso-occlusive crisis' – Robbin's.*

**Bone pain may by the presenting feature** *(H17th/638; Robbin's 7th/631)*

*Painful bone crisis may be the presenting feature.*

*This is extremely common in children and difficult to distinguish from acute osteomyelitis.*

**97. Answer is B (Bone pain):** Harrison 18th/p 855 *Harrisons 17th/638*

***'Recurrent episodes of painful crisis are the most common clinical manifestations'** – Harrisons 16th/ 596*

*Pain can develop almost anywhere in the body and may persist for a variable period. Among the options provided 'bone pain' is one such manifestation of 'painful crisis' and is thus the option of choice.*

*These painful crises are produced as a result of intermittent episodes of vasoocclusion in connective tissue and musculoskeletal structures producing painful ischaemia.*

**98. Answer is B (Malaria):** *Robbins 8th/387, 645; Robbins 7th / 402, 628*

***Heterozygous Sickle Cell Anemia confers protection against Malaria.***

**Sickle cell trait (HbS trait) confers resistance against Malaria in Heterozygotes** *(Robbins 7th / 402, 628)*

The possession of the sickle cell allele protects these individuals against malaria because the parasite dies when potassium leaks out of RBCs as they become sickle shaped.

***'HbS trait causes parasites to grow poorly or die at low oxygen concentrations** perhaps because of low potassium levels caused by potassium efflux from red cells on haemoglobin sickling' - Robbins*

*'In certain populations in Africa the prevalence of Heterozygosity is as high as 30%. This high frequency probably stems from **protection afforded by HbS against falciparum malaria'**. – Robbins 8th/645*

**99. Answer is A (HbA):** Harrison 18th/p 852, 854 *Harrison 17th edn /635, 637; Read text below*

***There are no β chains in sickle cell anemia (homozygos) and therefore no HbA ($\alpha_2\beta_2$)***

**Sickle cell anemia** is the prototype of *Structural Haemoglobinopathies* [Q] characterised by production of structurally abnormal Hb chain.

It is caused by substitution of valine for glutamic acid at position 6 of **β chains.** [Q]

**HbA is $\alpha_2\beta_2$**. It thus needs to have both α and β chains.

β chains however are defective in sickle cell disease such that:

- In hetrozygotes or sickle cell trait : 40% chains are defective
- In homozygotes or sickle cell disease : 100% chains are defective.

In other words ***there are no β chains in sickle cell anemia (homozygos) and therefore no HbA.***

**$HbA_2$ is $\alpha_2\delta_2$ and HbF is $\alpha_2\gamma_2$**

There is *no underlying defect in δ chains or γ chains in sickle cell disease and hence HbF and HbA2 may well be seen.*

**100. Answer is C (HbS is less than 50% and HbA has low affinity for HbS):** *Robbins 7th/629*

*The most important factor affecting the rate and degree of sickling is the amount of HBs and its interaction with other hemoglobin chains in the cell. Patients with sickle cell trait (heterozygotes) have 40% of haemoglobin in the form of HbS, the rest being HbA, which interacts only with HbS when deoxygenated.* ***Both the low concentration of HbS and the presence of interfering HbA act to prevent effective HBs aggregation and polymerization and thus red cells in sickle cell trait (heterozygotes) do not sickle.*** *– Robbins*

**101. Answer is A (0 and 100):** Harrison 18th/p 855 *Harrison 17th edn /638; Too obvious for reference*

***If the mother has sickle cell disease 'SS' and father is normal 'AA' all the offsprings will be 'SA'. Thus % of sickle cell disease (SS) will be zero and that of sickle cell trait (SA) will be 100%.***

Well the answer is fairly obvious but for those who still want an explanation, I will give it a try :

- Sickle cell disease is the homozygous state of HbS (SS) where S stands for gene coding HbS.
- Sickle cell trait is the heterozygous state of HbS (SA) where A stands for Absent gene.
- Normal individual has no gene for HbS (AA).

***If the mother has sickle cell disease 'SS' and father is normal 'AA' all the offsprings will be 'SA'. Thus % of sickle cell disease (SS) will be zero and that of sickle cell trait (SA) will be 100%.***

**102. Answer is D (Sickle cell Anemia):** *Robbins 7th/630; Outlines in pathology (2005)/80,82,199*

***Sickle cell Anemia is the single best answer of choice.***

*Crew cut appearance of skull and Gamma Gandy bodies in the spleen may be observed in several causes of hemolytic anemias but are most characteristic of sickle cell anemia amongst the options provided.*

***Crew cut appearance is most characteristic of Thalassemia and Sickle cell anemia.***

Crew cut appearance (Hair on End appearance)

- Thalassemia (Most charachteristic)
- Sickle cell Anemia (2nd most characteristic)
- Other Hemolytic anamias (May be seen)

*Hair on End appearance / crew cut appearance of skull results from expansion of marrow with bone resorption and secondary new bone formation because of compensatory hyperplasia of erythroid progenitors and may hence be seen in several causes of hemolytic anemias.*

**Gamma Gandy bodies are most characteristic of congestive splenomegaly but may be seen in hemolytic anemias especially sickle cell anemia**

Gamma Gandy bodies (calcium and hemosidrn deposits in spleen)

- Congestive spleenomegaly / portal hypertension. (most characteristics)
- *Hemolytic Anemias (Most characteristic of sickle cell anemia)*
- Hematochromatosis

**103. Answer is A (P. Falciparum):** *'Lecture Notes on Tropical Medicine' (John Wiley & Sons)2009/62*

***Sickle cell Anemia confers resistance against P. Falciparum.***

## Innate Traits that offer resistance against malaria

- ***The Sicke Cell Haemoglobin trait confers resistance against P. Falciparum*** [Q].
  *Individuals with sickle cell trait are resistant to the lethal effects of P. Falciparum. These individual may still develop infection with P. Falciparum but the trait prevents development of high parasitemia and prevents development of deadly complication of Falciparum malaria.*

> *There is now evidence that G-6PD difficiency and β thalassemia trait also offer resistance against P. falciparum but such evidence is less striking than with sickle cell trait.*

- ***The Duffy gene null allele confers resistance against P. vivax*** [Q].
  *Duffy antigens act as outside receptors for P. vivax. Without the Duffy antigens P. vivax canot intrude humans. This is believed to account for natural resistance of people of subsaharan African origin who lack the Duffy antigen*

## Hemoglobinopathies: Thalassemias

**104. Answer is A (Thalassemia)**

***Thalassemia is defined as a <u>quantitative defect</u> in synthesis of structurally normal globin chains***
*Sickle Cell Disease represents a qualitative defect in synthesis of globin chains (Structurally abnormal globin chains). G6PD Deficiency and Diamond-Blackfan Syndrome (Pure Red Cell Aplasia) are not associated with quantitative or qualitative defects in globin chain synthesis*

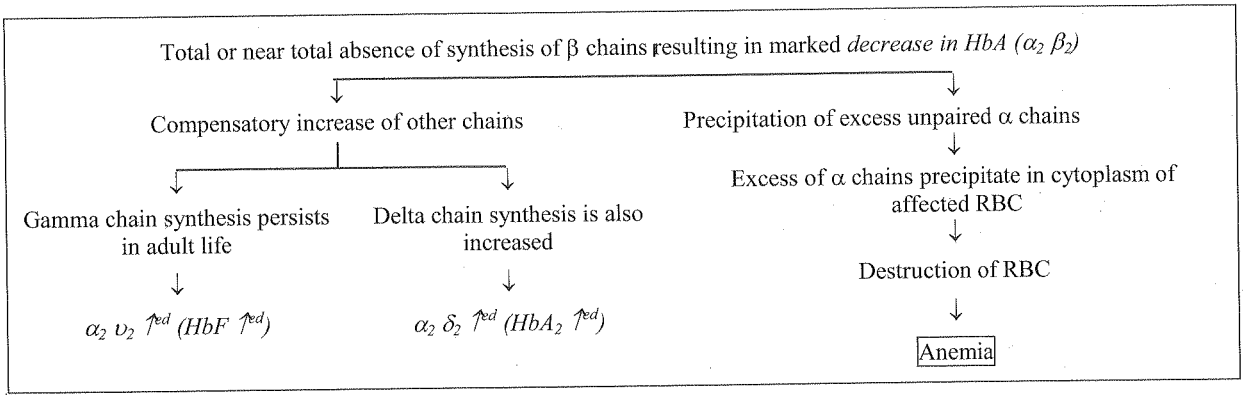
**105. Answer is B (Decrease in β chain, increase in alpha chain):** Harrison 18th/p 858, 859 *Harrison 17th edn /640,641; Robbins 7th/632*

*'The abnormality in Beta thalassemia is diminished synthesis of structurally normal Beta globin chains with unimpaired synthesis of alpha chains' – Robbins 7th/ 632*

**<u>Thalassemias</u>**

Characterized by *decreased rate of synthesis of Hb chains* [Q] that are *structurally normal* [Q].
β thalassemia or Cooley's anemia is the commonest thalassemia.

**<u>Characterized by</u>**:




**106. Answer is A (Intron-1):** *Hematology by Hoffman 4th/559,560*

*The most common mutation in beta thalassemia involves the intervening sequence 1 (IVS-1) or the intron-1*

<u>Mutations in Beta Thalassemia</u>

- Most types of Beta thalassemia are caused by point mutations affecting one or few bases.
- A given mutation usually occurs within only one racial group and within a given racial group, five or six specific mutations usually accounts for more than 90% of cases of Beta-thalassemia.
- ***The most common site of mutations in Beta thalassemia is the intervening sequence 1 (IVS-1) or Intron 1***

**107. Answer is B (Thalassemia intermedia):** Harrison 18th/p 859 *Harrison 17th/641; Nelson Pediatrics 16th/1479-1484; Nelson 17th/ 1630.*

***Presence of pallor and hepatosplenomegaly in a patient presenting late and capable of survival without blood transfusions is most suggestive of a diagnosis of thalassemia intermedia.***
***Due to abnormal synthesis of HbA, HbF is increased. (60-80%)***

**Clinical spectrum of Thalassemia (β thalassemia):**

| Syndrome | Thalassemia major (Serious homozygos form) | Thalassemia intermedia (They are also homozygos) | Thalassemia minor (heterozygos form) |
|---|---|---|---|
| General characteristic | • Presentation in early infancy with:<br>- Progressive pallor<br>- Hepatosplenomegaly<br>- Bony changes<br>• Invariably fatal during first few years of life if left untreated (Require repeated blood transfusions) | • Patient present somewhere between the two extremes with variable clinical manifestations of<br>- Progressive pallor<br>- Hepatosplenomegaly<br>- Bony changes<br>• These patients maintain hemoglobin levels between 6-10 g/dl and lead their life fairly comfortably. These patients may need occasional transfusions but are not dependent on blood transfusions for their survival. | • Presents late and patient can lead a practically normal life except for mild persistent anemia<br>• These patients are not dependent on blood transfusions |
| **Clinical Features** | | | |
| • Severity of disease | ++++ | ++ | ± |
| • Growth and development | Impaired | - | - |
| • Splenomegaly | ++++ | ++ | - |
| • Jaundice | ++ | +/- | - |
| • Skeletal changes | +++ | + | - |
| • Thalassemia facies | +++ | + | - |
| **Haematological findings** | | | |
| • Anaemia Hb gm/dl | < 7 (severe) | 7-10 (moderate) | >10 |
| • Microcytosis | +++ | ++ | + |
| • Hypochromia | +++ | ++ | + |
| • Basophilic stippling | ++ | + | + |
| • Anisopoikilocytosis | +++ | ++ | ± |
| • Target cells | +++ | ++ | + |
| • Nucleated red cells | +++ | +/- occasional | - |
| • Reticulocytes | 2-15 | 2-10 | < 5 |
| • HbF | 30-90% | 20-100% | 0-5% |
| • $HbA_2$ | <3.5% | <3.5% | 3.5-8% |
| • B.M. Iron | ++++ | ++ | ± |
| • Iron overload | + | - | - |
| • Life expectancy | 20-28 YEARS | Normal | Normal |

**108. Answer is C>D (Thalassemia Intermedia > Auto immune Hemolytic anemia):** *Harrisons 16th/612; Robbins 7th/634 Textbook of Emergency pediatric medicine 5th/934; Nelson 18th/2043*

***Both Thalassemia Intermedia and Autoimmune hemolytic anemias, may present with a haemoglobin of 5gm/dl in an adult patient. Adequate response with a single blood transfusion in the past favours a diagnosis of Thalassemia intermedia over AIHA, and is hence the single best answer of choice.***

***Thalassemia Intermedia*** *patients usually have a moderate hemolytic anemia with Haemoglobin levels between 6 to 10 gm/dl.Patients with thalassemia intermedia are not transfusion dependent and present later in life as they are capable of maintaining a haemoglobin level of greater than 6 gm without transfusion. However because of their constant dependence on a compensatory increase in red cell production, these patients are subject to exacerbations in their anemia (Hb<6gm/dl) during febrile or other illness, perioperatively or during pregnancy. Occasional blood transfusions in such patients may be required when there is a fall in the haemoglobin levels.*

***The patient in question is 21 years old and has a history of single blood transfusion in the past. He has now presented with a possible acute exacerbation of his anemia with a haemoglobin level of 5g/dl. His presentation is thus consistent with a diagnosis of thalassemia intermedia which is the single best answer of choice***

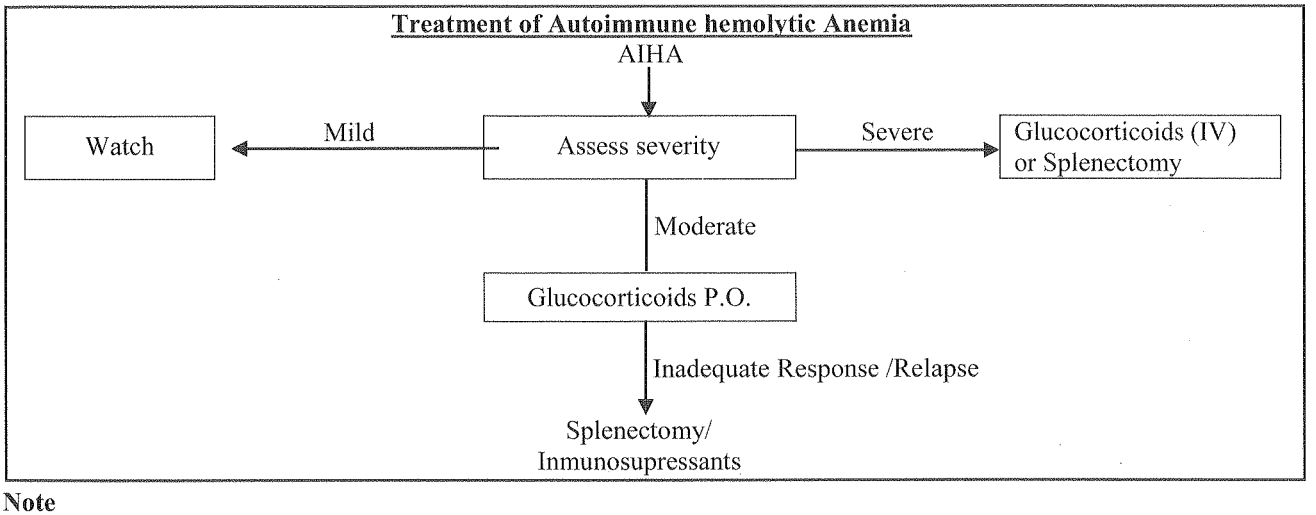
## Autoimmune Hemolytic Anemias

*Autoimmune Hemolytic Anemias may occur at all ages but are more common in adults. In many cases anemia is profound with haemoglobin levels < 6gm/dl*

*However patients with Auto immune hemolytic anemia are usually managed by glucocorticoids and not by blood transfusion. Such patients may be managed by blood transfusion if anemia is severe, but the patient is unlikely to stay asymptomatic after a single blood transfusion without receiving definitive therapy in the form of glucocorticoids splenectomy or immunosupressive medications*

*The patient in question is 21 years old and has presented to the emergency department with haemoglobin level of 5g/dl. This is consistent with a presentation of Autoimmune Hemolytic Anemia.*

*However the patient in question turned asymptomatic after receiving a single blood transfusion in the past which is unlikely with an autoimmune process. Thalassemia intermedia is therefore the better answer of exclusive.*




**Note**

*Patients with severe anemic may require blood transfusions that are usually only for transient benefits – Nelson*

***Thalassemia Minor*** *does not present with severe anemia with haemoglobin levels of 5g/dl. Thalassemia minor can therefore be excluded in this patient.*

***Thalassemia major*** *patients are transfusion dependent and require regular and multiple blood transfusion's by the time they reach 21 years of age thalassemia major can therefore be excluded in the patient*

| Syndrome | Genotype | Anemia | Treatment |
|---|---|---|---|
| Thalassemia Minor | Heterozygous | Mild Anemia or normal Hb (Hb > 10 gm /dl) Asymptomatic | No treatment |
| Thalassemia Intermedia | Homozygous | Moderate Anemia (Hb= 6-10 gm/dl) Present later in life (adolescent/adult) without need of regular transfusion | Intermittent transfusions during exacerbations of anemia. |
| Thalassemia Major | Homozygous | Severe anemia (Hb< 7gm/dl) Present in infancy | Regular blood transfusions |

**109. Answer is A (Thalassemia Trait):** *Harrison 18th/ 847; 17th/631, 640, 641; Hoffman 4th/575*

*Mild degree of Microcytic Anemia (MCV=70) with normal ferritin levels (100μg/L) suggests a diagnosis of thalassemia trait.*

| Parameter | Normal Index | Patient in question | Inference |
|---|---|---|---|
| Hb | Male: 14-18g/dl<br>Female: 12-16g/dl | Female with 10g/dl | *Mild Anemia* |
| Ferritin | 50-200 μg/dl | 100 μg/dl | *Normal* |
| MCV | 86-98 fl | 70 fl | *Microcytosis* |
| ***The patient in question has a microcytic anemia with normal ferritin levels*** | | | |

**Thalassemia trait and Iron deficiency anemia** may present with microcytic anemia, but Iron deficiency Anemia is associated with decreased Ferritin levels. The patient in question has normal / increased Ferritin levels and hence she is unlikely to have an iron deficiency anemia.

***The patient in question is thus most likely a patient of Thalassemia Trait***

| Parameter | Iron deficiency | Thalassemia Trait (Minor) |
|---|---|---|
| Smear | Microcytic Hypochromic | Microcytic hypochromic (Mild) |
| ***MCV (86-98 fi)*** | ↓ed | ↓ed |
| Serum iron | ↓ed (<30) | Normal |
| TIBC | ↑ed (>360) | Normal |
| Saturation | ↓ed (<10) | ↑ (30-80) |
| ***Ferritin*** | ↓ed (<15) | ↑ or (Normal Range in Minor/Trait) |

**Vitamin B12 deficiency and Folate deficiency cause Megaloblastic or Macrocytic anemia with increase MCV.**
*These anemias can be excluded as patient has a decreased MCV*

**110. Answer is D (Patient requires blood transfusion):** Harrison 18th/p 859 *Harrison 17th/641; Hoffman 4th/575*

*Most patients with β thalassemia trait are asymptomatic and have minimal or mild anemia. These patients do not require blood transfusions.*

**β Thalassemia Trait** (Thalassemia - Minor):

- Thalassemia Trait results from inheritance of single β thalassemia allele.
- Most patients are asymptomatic and do no require treatment.
- The Hemoglobin levels average 1-2g/d lower than that seen in normal persons.
- It results in mild hypochromic microcytic anemia

  Red cells are characteristically Hypochromic MCH < 26 pg
  Red cells are characteristically Microcytic MCV < 75 fl
- Smear shows varying number of target cells, prokaryocytes, ovalocytes and basophilic stippling
- Red cells protoporphyrin levels are normal (elevated in Iron deficiency anemia)
- Diagnosis is established in most cases by Hb electrophoresis

  ***HbA2 levels are elevated (usually upto twice the normal (normal = 1.5 – 3.5%))***
  ***HbF levels are elevated (may be normal <2% or moderately elevated 2.1 –5%)***
- Reticulocytes count is usually normal
- Osmotic fragility is decreased
- Most patients are asymptomatic and do not require any treatment.

**111. Answer is D (Severe anemia):** *Refer previous question*

*β Thalassemia trait is associated with mild anemia and not severe anemia.*

**Thalassemia Trait**

| Alpha Thalassemia Trait | Beta thalassemia trait (T. minor) |
|---|---|
| • *Normal $HBA_2$*<br>• *Normal HBF*<br>• Mild Anemia<br>- Mild Microcytosis<br>- Mild Hypochromia<br>• No need for Blood transfusion | • ↑ *$HBA_2$*<br>• ↑ *HBF*<br>• Mild Anemia<br>- Mild Microcytosis<br>- Mild Hypochromia<br>• No need for blood transfusion |

**112. Answer is D (Raised HbA2) : Multiple references**

***An abnormal increase in the level of HbA2 is the most significant parameter in the diagnosis of beta-thalassemia carriers.*** HbA-2 is constantly elevated in heterozygous carriers of β-thalassemia in all the ethnic groups studied. The values range from 3.5 to 7%. This increase appears to be determined by an increased output of δ-chains from both loci, in *cis* and *trans* to the thalassemia gene. *HbF is increased in half of the patients*, but the values observed are in general in the range of 1 to 3%.

***The hemoglobin electrophoresis with beta thalassemia trait typically has reduced levels of HbA, elevated levels of HbA2, and normal or increased levels of HbF.***
*Note: A normal concentration of HbA2 does not rule out beta thalassemia trait, especially if there is coexistent iron deficiency, which can lower HbA2 levels into the normal range.*

**113. Answer is C (Microcytosis):** *Harrison 18th/859; Harrison 17th/641*

*Alpha thalassemia trait exhibit mild microcytosis*
*HbF and HbA2 levels are normal and there is generally no anemia (mild anemia may be present)*
*'Persons with alpha thalassemia trait may exhibit mild hypochromia and microcytosis usually without anemia, HbA2 and HbF levels are normal' – Harrison 17th/641*

**114. Answer is A (Hereditary persistence of fetal hemoglobin):** *Harrison 18th/ 859; 17th/642; Nelson 17th/1630; CMDT 2005/467*

***Persistance of 95% of haemoglobin in the fetal form (HbF) in an adult who is asymptomatic and requires no blood transfusion suggests a diagnosis of hereditary persistence of fetal haemoglobin.***

*A combination of 95% HbF and 1.5% HbA2 may also be seen in Thalassemia intermedia. Although thalassemia intermedia does not require blood transfusion,* ***it is not asymptomatic.***

***Hereditary persistence of Fetal haemoglobin syndromes*** *are a form of thalassemia with decreased production of either or both β & δ globin chains.*

**The characteristic features are :**
- Continued synthesis of high levels of HbF in adult life.
- (A mutation lead to decreased synthesis of β and δ globins).
- Haemoglobin electrophoresis reveals only HbF
- Clinically the patient is asymptomatic
- Mild anemia and slight microsytosis may be preserved

**Hemoglobin levels in various thalassemias -** *CMDT*

| | Beta globin genes | HbA | $HbA_2$ | HbF |
|---|---|---|---|---|
| **Normal** | *Homozygous β* | **97-99 %** | **1-3%** | **< 1%** |
| **Thalassemia major** | *Homozygous $β^0$* | **0%** | **4-10 %** | **90-96 %** |
| **Thalassemia major** | *Heterozygous $β^+$* | **0-10 %** | **4-10%** | **90-96 %** |
| **Thalassemia Intermedia** | *Homozygous $β^+$ (mild)* | **0-30 %** | **0-10%** | **60-100%** |
| **Thalassemia minor** | *Heterozygous $β^0$* | **80-95 %** | **4-8%** | **1-5%** |
| | *Heterozygous $β^+$* | **80-95 %** | **4-8%** | **1-5%** |

***A combination of 95% HbF and 1.5% HbA2 may only be seen in Thalassemia intermedia***

**115. Answer is A (Haemoglobin electrophoresis) :** *Chandrasoma Taylor 2nd/386*

***Presence of hypochromic microcytic anemia. Target cells on peripheral smear and positive family history suggest a diagnosis of Thalassemia.***

***Hemoglobin electrophoresis should always be the first investigation to include/exclude thalassemias.***

**Thallassemia**

- Thallassemias are characterised by *decreased rate of synthesis*[Q] of Hb chains that are *structurally normal*[Q]
- Thallassemia symdromes are common in persons with Mediterranean, African, Asian ancestary and *show marked familial tendencies*[Q]
- **β thallassemia or *Cooley's anemia***[Q] is the *commonest type*[Q]
- β thallassemia major is characterised by
  - Total or near total absence of synthesis of β chains, resulting in marked ***decrease in HbA ($\alpha_2\beta_2$) levels***[Q]
  - Gamma chain synthesis then persists into adult life resulting in ***elevated HbF ($\alpha_2\gamma_2$) levels*** [Q]
  - Delta chain synthesis is also increased to compensate for β chains resulting in ***elevated $HbA_2$ ($\alpha_2\delta_2$) levels***[Q]
- Excess free α chains precipiate in cytoplasm of affected RBC and result in their destruction which contributes to ***anemia (decreased Hb).*** [Q]
- The peripheral blood picture shows : - ***Microcytic hypochromic anemia*** [Q]
  - Anisocytosis (marked) [Q]
  - ***Target cells (numerous)*** [Q]
  - Reticulocytosis and nucleated red cells. [Q]
- Diagnosis is ***established by Haemoglobin electrophoresis*** which shows : [Q]
  - Elevated HbF and $HbA_2$ with greatly decreased or absent HbA.

***Target cells*** *are formed due to increased ratio of RBC surface area to volume. Seen in Haemoglobin disorders such as: Thallassemia, HbS, HbC etc, Liver disease.*

**116. Answer is D (Hb-electrophoresis):** Harrison 18th/p 854, 859 *Harrison 17th edn /637, 641; Read text below*

***Hemoglobin electrophoresis documenting elevated HbF & $HbA_2$ with greatly decreased or absent HbA point towards a diagnosis of β thalassemia.***

- ***Thalassemia is a quantitative defect in Hb characterized*** by lack of certain types of globin chains and compensatory increase in other globin chains.
  Electrophoretic techniques used for routine hemoglobin analysis help in quantification and identification of various hemoglobins.
- Thalassemia, the commonest thalassemia for example can be detected by electrophoretic demonstration of the following characteristics:
  *Total absence of synthesis of β chain : Marked decrease in HbA ($\alpha_2\beta_2$)*
  *Compensatory increase of α & delta chains : ↑HbF ($\alpha_2\upsilon_2$); ↑$HbA_2$ ($\alpha_2\delta_2$)*

**117. Answer is C (Hb electrophoresis) :** Harrison 18th/p 854, 859 *Harrison 16th/599, 608; Harrison 17th edn /637, 641; CMDT 2005/466; CMDT 09/432*

***'The diagnosis of thalassemia syndromes is best established by Hb electrophoresis.'***

*Thalassemia is a quantitative defect in Hb characterized by lack of certain types of globin chains and compensatory increase in other globin chains. These changes form the basis of electrophoretic investigations and are diagnostic of respective thalassemia syndromes.*

***NESTROFT test :*** *Naked Eye Single Tube Red Cell Osmotic Fragility Test is used for screening of thalassemia but is not diagnostic.*

***HBAIC :*** Estimation of glycated haemoglobin is used for estimating long term Glucose control in diabetics. It has no role in thalassemia.

***Target cells*** **:** May be seen in thalassemia but do not establish diagnosis of thalassemia.

| Target Cells |
|---|
| Thalassemia |
| Haemoglobin C, s etc. |
| Liver diseases |

**118. Answer is A (Thalassemia):** *IAP Color Atlas of Pediatrics (JP Medical Ltd, 2012)/*

***NESTROFT Test is a screening test used for screening of Beta Thalassemia trait.*** *NESTROFT Test is only a screening test and should always be followed by Hemoglobin electrophoresis for evaluation of HBA2. The only confirmatory test for diagnosis of Beta Thalassemia is HBA2 estimation.*

NESTROF Test : Naked Eye Single Tube Red Cell Osmotic Fragility Test

- NESTROF Test is a screening test typically used for the diagnosis of Beta Thalassemia Minor/Trait

  A positive NESTROF Test is seen in several other conditions besides β-thalassemia minor/ trait
  It is also seen like α- thalassemia trait, HbE, HbS and Hereditary Persistence of Fetal Haemoglobin (HPFF).
- NESTROF Test has been found to have a high sensitivity (80.7-100%) and high negative predictive value (96-100%).
- Negative NESTROF Test negative rules out thalassemia minor.
- NESTROF Test has low specificity and is not a confirmatory procedure .
- NESTROF Test should always be followed by Hemoglobin electrophoresis for evaluation of HBA2

**119. Answer is A (Hb electrophoresis):** Harrison 18th/p 854, 859 *Harrison 17th/637, 641; Nelson Pediatrics 16th/1479-1484; Nelson 17th/1630*

***Progressive increasing pallor along with hepatosplenomegaly in a five year old girl is consistent with a diagnosis of thalassemia. (Thalassemia intermedia)***

***'Haemoglobin electrophoresis' is the test of choice for diagnosing this condition and hence is the option of choice here.***

*Medullary and extramedullary erythropoiesis leads to expansion of bone marrow space causing a characteristic hemolytic facies with frontoparental, occipital bossing, malar prominence and malocclusion of teeth and complications that include distortion of ribs and vertebra, pathological fractures of the long bones, splenomegaly and its complications – hypersplenism, hepatomegaly gallstone and leg ulcers.*

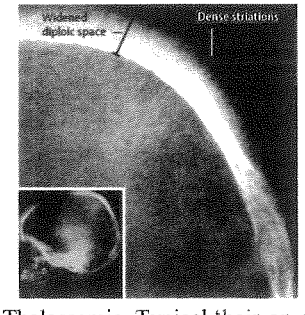
**120. Answer is A (Thalassemia):** *Essential Radiology (2006)/536; Rudolph Pediatrics 21st/1537; Musculoskeletal Imaging by Bohndorf (2001)/214*

***Hair on end appearances may be seen in both sickle cell anemia and thalassemia, but it is more characteristic of thalassemia major which is the single best answer of choice***

Hair on End appearances (Crew cut appearance) of the cranial vault

- Hair an end appearance refers to the presence of multiple vertical striations through expanded marrow (widened diploic space) as a result of subperiosteal bone growth in a series of vertical striations
- This is produced as a result of marrow hyperplasia and may be observed in conditions.
- Associated with marrow hyperplasias secondary to hemolytic anemia.
- ***Its presence is considered characteristic of thalassemia but it may also be seen in sickle cell anemia and other causes of hemolytic anemia including hereditary spherocytosis and G-6PD deficiency.***

Hair on end appearance is also called crew cut appearance




Thalassemia. Typical 'hair-on-end' skull

**121. Answer is D (Alpha Thalassemia silent carrier):** *Multiple references; Refer text below*

***Deletion of one alpha globin gene on one chromosome is best defined as Alpha Thalassemia silent carrier state.***

| | |
|---|---|
| Alpha-thalassemia silent carrier (-α/αα) | Results from a deletion or "non-deletion" mutation that inactivates one of the two α-globin genes ***on one chromosome*** |
| Alpha-thalassemia trait (--/αα) or (-α/-α) | **Alpha thalassemia -1- trait or α° thalassemia trait**<br>Results from deletion or inactivation of two α-globin genes in cis configuration (--/αα).<br>When both α-genes on a chromosome are deleted (--/αα) or inactivated, the condition is called α°-thalassemia (no output of α-globin from the chromosome). Previously, α° thalassemia was called α-thalassemia-1-trait.<br>**Alpha thalassemia-2-trait or α+ thalassemia trait**<br>Results from deletion or inactivation of two α-globin genes in trans configuration (-α/-α).<br>When one α-gene on each chromosome is deleted or inactivated by a mutation the condition is called α+ thalassemia (previously known as α-thalassemia-2-trait). In this case, some α globin is produced from each chromsome |
| Hb-H disease (--/-α) | Results from deletion or inactivation of three α-globin genes<br>This is usually as a result of the compound heterozygous state for α°-thalassemia and α+-thalassemia.<br>Patients accumulate beta chains and may form beta chain tetramers called Hb-H(β4) |
| Hb Barts (--/--) | Results from deletion of four α-globin chains and rarely may involve non-deletion defects. Fetal blood contains mainly Hb Bart (γ4) and 10%-15% of the embryonic hemoglobin Portland (ζ2γ2).(Deletion or inactivation of all four α-globin chains makes it impossible to assemble HbF and HbA) |

| Genes encoding alpha thalassemia's |
|---|
| HBA1, encoding α1-globin, and HBA2, encoding α2-globin, are the two genes associated with α-thalassemia. They are localized to the telomeric region of chromosome 16p. HBA1 is the α1 gene while HBA2 is the α2 gene |

**122. Answer is B (Hb Barts) :** *Multiple references; Refer text below*

***Hb Barts (Hydrops Fetalis) results from deletion of four α-globin chains***

| Alpha-Thalassemia | Number of Gene Deletions | Genotype |
|---|---|---|
| Silent carrier state | 1 gene deletion | (-α/αα) |
| α thalassemia trait | 2 gene deletion | (--/αα) or (-α/-α) |
| HbH disease | 3 gene deletion | (--/-α) |
| Hb Barts | 4 gene deletion | (--/--) |

**123. Answer is A (Deletion of three alpha genes):** *Harrison's 18th/ 859*

***HbH is characterized by deletion of three alpha chain genes.***

**124. Answer is B (Alpha2 Gamma2):** *Wintrobe's Hematology 13th/108*

***Fetal Hemoglobin is represented by Alpha-2; Gamma-2 Hemoglobin chains.***

| Hemoglobin Type | Hemoglobin Chains | Normal Adult Values |
|---|---|---|
| Fetal Hemoglobin (HBF) | α2γ2 (Alpha 2 Gamma 2) | <2percent of Total Adult HB |
| Adult Haemoglobin (HBA) | α2β2(Alpha 2 Beta 2) | ~96 percent of Total Adult HB |
| Adult Hemoglobin (HBA2) | α2δ2(Alpha2 Delta 2) | <3.5percent of Total Adult HB |
| HemoglobinBarts | γ4 (Gamma 4) | Nil |

**125. Answer is C (Zeta 2; Gamma 2) :** *Multiple references; Refer text below*

*Hemoglobin Portland (I) is a form of embryonic hemoglobin existing at low levels during embryonic and fetal life, composed of two zeta chains and two gamma chains.*

| Embryonic hemoglobin |
|---|
| *Gower 1- zeta(2), epsilon(2)*<br>*Gower 2- alpha(2), epsilon (2)*<br>*Portland 1- zeta(2), gamma (2)*<br>*Portland 2 – zeta(2), beta(2)* |

| Fetal hemoglobin |
|---|
| *Hb F- alpha(2), gamma(2)* |

| Adult hemoglobin |
|---|
| *Hb A- alpha(2), beta(2)*<br>*HB A2- alpha(2), delta(2)* |

| | ζ chain (Zeta Chain) | α chain (Alpha Chain) |
|---|---|---|
| ε chain (Epsilon) | **HbE Gower 1** | **HbE Gower 2** |
| γ chain (Gamma) | **HbE Portland I** | HbF |
| β chain (Beta) | **HbE Portland II** | HbA |
| δ chain (Delta) | N/A | HbA2 |

Hemoglobin H (HbH). Four β-globin chains (β4).
Hemoglobin Bart (Hb Bart). Four γ-globin chains (γ4).

**126. Answer is A (Juvenile CML):** *Ghai 6th/569; Interpretation of diagnostic tests 8th/411, 412*

*Fetal Haemoglobin levels (HbF) are increased in most cases of Juvenile CML – Ghai 6th/569*

Causes of Raised HbF levels (Interpretation of Diagnostic Test 8th/411, 412)

- Haemoglobinopathies
  - β thalassemia major
  - β thalassemia minor
  - Sickle cell disease
- Hereditary Persistance of HbF
- Anemia:
  - Non Hereditary refractory normoblastic anemia
  - Pernicious anemia
  - Aplastic anemia
- ***Leukemia specially Juvenile Myeloid Leukemia***
- Multiple myeloma
- Molar pregnancy
- Patients with Trisomy 13 or Trisomy 21 (Down's syndrome)
- Some chronic viral infections (eg CMV, EBV)

**127. Answer is A (Alpha Thalassemia):** *Disorders of Hemoglobin 1st (2001)/212, 213*

*Alpha Thalassemia are associated with reduced levels of HbA2*

Causes of Increased HbA2 levels

- *Beta thalassemia*
- *Sickle cell anemia*
- *Megaloblastic anemia*
- *Hyperthyroidism*
- *Unstable Hemoglobinopathies*
- *Malaria (doubtfull cases)*

Causes of Decreased HbA2 levels

- *Iron deficiency Anemia*
- ***Alpha thalassemia***
- *Delta thalassemia*
- *Sideroblastic anemia*
- *Myelodysplastic syndromes*
- *Acute myelocytic leukemia (minor reduction)*
- *Hb Lepore*

**128. Answer is D (Penicillamine) :**

*Penicillamine is not used for Iron Chelation. Penicillamine is a chelating agent most commonly used for removal of excess free copper from the body in patients with Wilson's disease.*

**Kelfer, Desferal and Deferiprone are all commonly used agents for iron chelation**

| Iron Chelating Agents for Hemoglobinopathies |
|---|
| *Deferoxamine* (Desferal) |
| *Deferasirox* (Exjade, ICL-670) |
| *Deferiprone* (Kelfer, Ferriprox) |

| **Properties of iron chelating agents** | | | |
|---|---|---|---|
| **Feature** | **Deferoxamine (Desferal)** | **Deferiprone (Kelfer, Ferriprox)** | **Deferasirox (ICL-670 ; Exjade)** |
| Iron binding efficiency (drug: iron) | 1.1 | 3:1 | 2:1 |
| Iron selectivity | Highly selective | Zinc is also excreted | Highly selective |
| Regimen | SC or IV infusion | Oral, 3 times a day | ***Oral, once a day*** |
| Tolerability | Local reactions | Joints problems | Skin rashes |
| Long-term safety profile | Proven | Severe neutropenia | Unproven |



## Autoimmune Hemolytic Anemia

**129. Answer is D (Mycoplasma Pneumonia):** *Harrison 18th/ 882; 16th/612, 613, 614; 17th/ 660; API 8th edn/ 810, 811*

*Mycoplasma pneumoniae infections are associated with a cold antibody haemolytic anemia*

**Autoimmune hemolytic anemias** are characterized by formation of autoantibodies against patient's own red cells.

Depending upon reactivity of autoantibodies these are further divided into two types.

| ***Warm Antibody Hemolytic Anemia*** | ***Cold Antibody Hemolytic Anemia*** |
|---|---|
| • Antibodies here bind with antigens (on RBC) at body temperature (37°C)<br>• These antibodies are called warm antibodies and are **nearly IgG** (Rarely IgM or IgA) | • Antibodies here bind with antiens (on RBC) better at temperatures lower than 37°C<br>• These antibodies are called cold reactive antibodies and are **usually IgM**<br>[An exception is cold reactive antibodies of IgG$^{Q}$ type (***Donath Landsteiner Antibody***) in Paroxysmal cold hemoglobulinuria] $^{Q}$ |
| ***Causes*** | ***Causes*** |
| 1. Idiopathic<br>2. Lymphomas: CLL $^{Q}$, Non-Hodgkins, etc<br>3. SLE $^{Q}$ and other Collagen Vascular Diseases<br>4. Drugs: eg. α Methyldopa $^{Q}$ | 1. Acute: Mycoplasma infection $^{Q}$ Infectious mononucleosis $^{Q}$<br>2. Chronic : Idiopathic $^{Q}$<br>3. Paroxysmal cold hemoglobinuria $^{Q}$ |
| ***Mechanism of Hemolysis*** | ***Mechanism of Hemolysis*** |
| Human red cells cooled with IgG are trapped by splenic macrophages – red cell destruction | Antibodies of IgM type bind on Red cell surface and cause agglutination. Hemolytic effect is mediated through fixation of C3 to RBC surface. $^{Q}$ |
| ***Diagnosis*** | ***Diagnosis*** |
| Positive direct Coomb's test, at 37°C for presence of warm antibodies on surface of Red cell. $^{Q}$<br>Positive Indirect Coomb's test at 37°C for presence of large quantities of warm antibodies in serum. $^{Q}$ | Positive direct Coomb's test for detection of C3 on the red cell surface but IgM responsible for coating on red cells is not found. $^{Q}$ |

**130. Answer is A (IgM antibodies) :** Harrison 18th/p 882 *Harrison 17th/660 , Harrison 16th/613, 612*

*Antibodies that bind with antigens better at temperature lower than 37°C are called Cold reactive antibodies. These antibodies are usually IgM antibodies.*

***IgM cold- reacting antibodies readily agglutinate RBC's and are called cold agglutinins.***

**Note**

*Donath Landsteiner antibody of Paraxysmal Cold Haemoglobinuria is a rare IgG type of cold reactive antibody. But the term 'cold agglutinins' is generally used for only the IgM cold reacting antibodies that readily agglutinate Red Blood cells*

*'IgM Cold reacting antibodies readily agglutinate RBC and are called cold Aglutinins' - Harrisons 16th/613*

***IgM antibody is therefore the single best answer of choice.***

**131. Answer is B (Chronic lymphatic leukemia):** *Harrison 18th/p 882; 16th/ 612; Harrison 17th/ 660; API 8th edn/ 810, 811*

*Leukemias especially of the CLL type are associated with Autoimmune hemolytic anemia – Harrison*

**Hemolysis due to Antibodies:**

| Warm-Antibody immunohemolytic anemia | Cold-Antibody immunohemolytic Anemia |
|---|---|
| 1. Idiopathic<br>2. Lymphomas: Chronic lymphocytic leukemia, non-Hodgkin's lymphomas, Hodgkin'd disease (infrequent)<br>3. SLE and other collagen-vascular diseases<br>4. Drugs<br>(a) α-Methyldopa type (autoantibody to Rh antigens)<br>(b) Penicillin type (stable hapten)<br>(c) Quinidine type (unstable hapten)<br>5. Postviral infections<br>6. Other tumors (rare) | 1. Cold agglutinin disease<br>(a) Acute: Mycoplasma infection, infectious mononucleosis<br>(b) Chronic: Idiopathic, lymphoma<br>2. Paroxysmal cold hemoglobinuria |

**132. Answer is B (B cell type) :** Harrison 18th/p 926, 927 *Harrison 16th 648, 612; 17th/ 693; CMDT 2006/495, 506; CMDT 2008/449; 09/455*

*The diagnosis of typical B cell CLL should be considered in a patient presenting with an autoimmune hemolytic anemia or autoimmune thrombocytopenia. – Harrison 16th / 648*

***Autoimmune hemolytic anemia (AIHA) and Lymphoid malignancies***

*Autoimune hemolytic anemias may be seen in association with Leukemias specially of the B cell CLL type and with Lymphomas especially of the Non Hodgkins type.*

| Leukemias and AIHA | Lymphomas & AIHA |
|---|---|
| Characteristically seen in association with Chronic Lymphocytic Leukemia (***Typical B cell CLL***)$^{Q}$<br>*(CLL is a clonal malignancy of B cell)*$^{Q}$ | More commonly seen in association with Non Hodgkin's Lymphoma, but may also be seen with Hodgkins type.<br>***Non Hodgkins(NHL) > Hodgkins (infrequent)*** |
| Autoantibodies are mainly ***IgG type***$^{Q}$ and hemolytic anemias are accordingly classified as ***warm antibody type*** | Autoantibodies are *usually IgG* (warm antibodies) but cold Antibody type (IgM) hemolytic anemias may also be seen .<br>*Warm antibody type > Cold Antibody (infrequent) type* |

**133. Answer is C (CLL):** *Harrison 14th/ 666; Harrison 16th/ 612; Refer previous question*

*Leukemias specially of the CLL type are associated with Autoimmune hemolytic anemia - Harrison*

*Autoimmune hemolytic anemia of the warm antibody type are caused by leukemias specially of the chronic lymphocytic type & Non Hodgkin lymphoma*

**134. Answer is A (Alcoholic cirrhosis):** *Harrison 16 th edn/ 612; API 8th edn/ 810, 811; Read text below*

*Coomb's positive hemolytic anemia may be seen in autoimmune conditions. All options other than alcoholic cirrhosis may have autoimmune etiologies and hence, may very well have coomb's positive haemolytic anemia as a feature.*

*Anemias which occur due to autoimmune destruction of RBCs are called autoimmune hemolytic anemia. The autoimmune destruction of RBC's is caused by the presence of autoantibodies against R.B.C.*

*Coomb's test is used to detect the presence of these autoantibodies.* ***So autoimmune hemolytic anemias are also known as coomb's positive hemolytic anemias.***

**135. Answer is C (SLE):** *Harrison 16th/612; API 8th/810; Hoffman's 4th/693, 695*

*Coombs positive hemolytic anemia is a feature of autoimmune hemolytic anemia and is characteristically seen in SLE.*

**Polyarteritis Nodosa (PAN)** may also be associated with a Coombs positive hemolytic anemia. However this association is rare, and more commonly patients with PAN present either with an anemia of chronic disease or a microangiopathic hemolytic anemia.

**TTP and HUS** are characteristically associated with Coombs negative microangiopathic hemolytic anemias.

**136. Answer is A (Thrombotic Thrombocytopenic Purpura):** *Harrisons 16th/612; API 8th/810*

*Thrombotic Thrombocytopenic purpura is associated with Coombs negative hemolytic anemia.*

***Coomb's positive hemolytic anemia is a feature of Autoimmune Hemolytic anemias**, SLE and other collagen vascular diseases including PAN, and scleroderma may be associated with warm antibody autoimmune hemolytic anemias and hence may present with Coomb's positive hemolytic anemia.*

***Thrombotic Thrombocytopenic purpura is not associated with immune mediate hemolysis and hence it is associated with Coomb's negative hemolytic anemia***

Collagen vascular diseases associated with Autoimmune Hemolytic Anemias (AIHA) (Warm Antibody Type)

| Common | Less Common/Rare |
|---|---|
| *SLE* | • Rheumatoid Arthritis<br>• PAN<br>• Scleroderma<br>• Sjogren's syndrome |

**137. Answer is C (systemic lupus erythematosis) :** *Harrisons 16th/612; Hoffman's 4th/693,695*

*Coomb's positive hemolytic anemia is a feature of autoimmune vascular disease and may also be seen in SLE and other Collagen Vascular diseases including PAN and Systemic sclerosis.*

***However amongst the options provided coombs positive hemolytic anemia is most commonly associated with SLE which is the single best answer of exclusion.***

*Autoimmune hemoletic anemias are associated with 'collagen vascular diseases especially systemic lupus Erythematosis'– Harrisons*

*Autoimmune hemolytic anemia are associated with 'autoimmune diseases particularly Systemic Lupus Erythematosis' -Hoffman.*

**138. Answer is C (Coomb's test) :** *Harrison 18th/p 875, 881; 17th/ 634, 635, 659, Harrisons 16th/ 608, 609; CMDT 09/436*

*Presence of anemia and jaundice together with spherocytes in peripheral smear is consistent with a diagnosis of both hereditary spherocytosis and auto immune hemolytic anemias.*

*The onset of symptoms at 40 years of age favours an acquired etiology and suggests a presumptive diagnosis of Acquired Autoimmune Hemolytic anemias. Nevertheless, mild cases of Hereditary spherocytosis may also first present in young adults and even later in life (Harrison)* ***Coomb's test is the single best investigation for such patients as it can clinch the diagnosis of Autoimmune Hemolytic anemias and establish the distinction between the two probable diagnosis.***

According to Harrison text:

***'Hereditary spherocytosis must be distinguished primarily from the spherocytic hemolytic anemias associated with RBC antibodies'***

***Coomb's test is positive in immune spherocytic hemolytic anemias and it is negative in hereditary spherocytosis***

- "The diagnosis of immune spherocytosis is readily established by a positive coomb's test" – Harrison
- "Coomb's test is negative in hereditary spherocytosis" CMDT 06

***Osmotic fragility*** *test will be positive in both hereditary spherocytosis and immune spherocytic hemolytic anemias.*
*"Increased osmotic fragility merely reflects the presence of spherocytes and does not distinguish hereditary spherocytosis from other spherocytic hemolytic disorders such as autoimmune hemolytic anemia" – CMDT 06/491*

***Coomb's test*** *is the single best next investigation here as it will* ***establish the distinction***.

**Note: Presence of spherocytes in the peripheral blood smear does not necessarily imply hereditary spherocytosis**

| *Causes of spherocytosis in peripheral smear / Spherocytic hemolytic anemia* |
|---|
| • Hereditary spherocytosis |
| • Immunohemolytic anemias (Autoimmune hemolytic anemias) |
| • In association with hemolysis induced by splenomegaly in patients with cirrhosis |
| • Clostridial infections |
| • Certain snake envenomations |
| • G6PD deficiency (few spherocytes) |

**139. Answer is C (Coombs test) :** Harrison 18th/p 851, 852, 879 *Harrison 17th/ 654, 655, 659;API 8th/809, 810, CMDT 2008 / 430, 431; CMDT 09/436*

*Presence of anemia and jaundice together with spherocytes in peripheral smear is consistent with the diagnosis of both 'hereditary spherocytosis' and 'immunohemolytic anemias'.* ***Coomb's test*** *is the single best next investigation here as it will* ***establish the above distinction.***

According to Harrisons text:
***'Hereditary spherocytosis must be distinguished primarily from the spherocytic hemolytic anemias associated with RBC antibodies.'***

***Coomb's test is positive in immune spherocytic hemolytic anemias and it is negative in hereditroy spherocytosis.***
- *"The diagnosis of immune spherocytosis is readily established by a positive coomb's test." - Harrison*
- *"Coomb's test is negative in hereditary spherocytosis." CMDT 06*

***Osmotic fragility*** ***test will be positive in both hereditary spherocytosis and immune spherocytic hemolytic anemias.***

*"Increased osmotic fragility merely reflects the presence of spherocytes and does not distinguish hereditary spherocytosis from other spherocytic hemolytic disorders such as autoimmune hemolytic anemia." - CMDT 06 / 491*
***Coomb's test*** *is the single best next investigation here as it will* ***establish the above distinction.***

**Causes of spherocytes in peripheral smear / Spherocytic hemolytic anemia**
- Hereditary spherocytosis.
- Immunohemolytic anemias (Autoimmune hemolytic anemias).
- In association with hemolysis induced by splenomegaly in patients with cirrhosis.
- Clostridial infections.
- Certain snake envenomations.
- G6PD deficiency (few spherocytes).

**140. Answer is C (Haemolytic disease of the newborn)**

***Hemolytic disease of newborn*** *is an immune mediated anemia resulting from maternal* ***antibodies against blood group antigens*** *on foetal red blood cells.*

**141. Answer is C (Haemolytic disease of the newborn)**

***Hemolytic disease of newborn is an immune mediated cause of anemia resulting from maternal antibodies against blood group antigens on fetal red blood cells. Diagnosis is suggested by the presence of neonatal hemolytic disease and a positive Direct Antiglobulin Test (DAT)***
Diamond Blackfan anemia or congenital pure red cell aplasia is a non-immune and non-haemolytic anemia resulting from failure of red cell production. Hereditary Spherocytosis (Membrane defect) and G-6-PD deficiency are both non-immune causes of Hemolytic anemias.

**142. Answer is D (Haemolytic disease of the newborn)**

*Hemolytic disease of newborn is an immune mediated cause of anemia resulting from maternal antibodies against blood group antigens on fetal red blood cells. Diagnosis is suggested by the presence of neonatal hemolytic disease and a positive Direct Antiglobulin Test (DAT)*

*Diamond Blackfan anemia or congenital pure red cell aplasia is a non-immune and non-haemolytic anemia resulting from failure of red cell production. Hereditary Spherocytosis (Membrane defect) and G-6-PD deficiency are both non-immune causes of Hemolytic anemias*

**Hemolytic disease of the fetus and newborns (HDFN)**

Results from the destruction of red blood cells by maternal immunoglobulin (Ig-G antibodies) that gain access to the fetal circulation during pregnancy. These antibodies may be directed against Rhesus (Rh) or other blood group antigens on fetal red blood cells, inherited from the father and not present on the mother's red blood cells. HDFN associated with blood group antibodies has a broad spectrum of effects, ranging from mild anemia and hyperbilirubinemia in an infant to life-threatening complications before birth.

**Immune Hemolytic Anemia Due to Maternal Disease**

Maternal autoimmune hemolytic anemia or lupus erythrematous during pregnancy may be associated with passive transfer of IgG antibody to the fetus. The diagnosis is suggested by the presence of neonatal hemolytic disease, a positive DAT, absence of Rh or ABO incompatibility, and antiglobulin-positive hemolysis in the mother. Treatment with prednisone in the mother may reduce both maternal hemolysis and the risk of neonatal morbidity. As in other cases of neonatal hemolysis, attempts are made to prevent hyperbilirubinemia and Kernicterus



## Microangiopathic Hemolytic Anemia

**143. Answer is C (Hemophilia - A):** *Harrison 18th/ 883; 17th/658; CMDT 2007/533; 2009/442, 436; William's Manual of Hematology 6th/118*

*Hemophilia A is not a cause for microangiopathic hemolytic anemia or fragmented RBC's in peripheral blood.*

**Classification of Microangiopathic Hemolytic Anemia**

**Primary**

- **Thrombotic thrombocytopenic purpura**
- **Hemolytic uremic syndrome**

**Secondary**

- **Associated with disseminated intravascular coagulation**
  - Infections (sepsis)
  - Shiga-type toxins
  - HIV
  - Snake venoms
  - Abruptio placentae
- **Associated with hypertension**
  - Malignant hypertension
  - Preclampsia, eclampsia,
  - HELLP syndrome
- **Associated with malignancy**
  - Adenocarcinomas; gastrointestinal, breast, lung
- **Associated with drugs and/or radiation**
  - Antineoplastic agents
  - Radiation nephritis and chemotherapy in organ transplantation
  - Ticlopidine
- **Associated with immunologic disorders/Vasculitis**
  - Acute glomerulonephritis
  - SLE
  - Polyarteritis nodosa
  - Scleroderma
  - Other vasculitis

- **Associated with congenital malformations**
  - Cavernous hemangioma (Kasabach-Meritt syndrome)
  - Hemangioendothelioma of the liver
- **Associated with antiphospholipid syndrome** (*NMS Medicine*)
- **Associated with Prosthetic valves** (*Harrison/CMDT*) (Pathologically Macroangiopathic – *Rubin's Pathology*)

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**144. Answer is D (Evan's syndrome):** *Wintrobe's Hematology 12th/968; Harrison 17th/658; Harrison 18th/881; William's Obstetrics 21st/577*

***Evan's syndrome is not a microangiopathic hemolytic condition and does not present with fragmented RBCs in the peripheral smear.***
*Presence of fragmented RBC's in the peripheral smear suggests the diagnosis of a micro-angiopathic process (Microangiopathic Hemolytic Anemia). The fragmentation of RBC's is caused by fibrin deposits in small blood vessels, which cause mechanical hemolysis. Patients with microangiopathic hemolytic anemias are usually thrombocytopenic (due to consumption of Platelets).*

***Microangiopathic Hemolytic anemia (fragmented RBC) and Thrombocytopenia are typically seen in TTP, HUS, DIC and HELLP syndrome besides several other conditions.***

**Evan's syndrome (combination of ITP and Autoimmune Hemolytic Anemia (AIHA))**

- *Evan's Syndrome refers to a combination of Idiopathic Thrombocytopenic Purpura (ITP) and Autoimmune Hemolytic Anemia (AIHA) in the absence of an underlying cause / disease.*
- The occurence of thrombocytopenia may coincide with episodes of hemolysis or may arise as separate episodes.
- Evan's syndrome is more common in children
- Evan's syndrome tends to be resistanct to management of Warm AIHA or ITP
- ***Evans syndrome presents with 'Thrombocytopenia' and 'Immune Hemolysis'.***

***Evan's syndrome does not present with microangiopathic features or fragmented RBCs.***

**TTP, DIC and HELLP syndrome all may present with microangiopathic features (fragmented RBC's) and thrombocytopenia**

| Microangiopathic Hemolytic Anemias |
|---|
| • *TTP* |
| • *HUS* |
| • *DIC* |
| • *Vasculitis (Collagen Vascular Disorders)* |
| • *Malignant Hypertension/Eclampsia/**HELLP*** |
| • *Disseminated carcinomatosis (Metastasis)* |
| • *Drugs / Radiation* |
| • *Antiphospholipid syndrome*(*NMS Medicine*) |
| • *Prosthetic Heart Valves* (Pathologically Macroangiopathic – *Rubin's Pathology*) |

***Patients with microangiopathic hemolytic anemias are usually thrombocytopenic*** *(due to consumption of Platelets).*

**145. Answer is C (Myocardial Infarction):** Harrison 18th/p 883 *CMDT 2007/533; 2009/442, 436; Harrison 17th/658; William's Hematology 6th/118*

***Myocardial Infarction is not a cause for microangiopathic hemolytic anemia.***

**146. Answer is None or B (None or Metallic Heart Valve):** *Rubin's Pathology 5th/878; William Manual of Hematology Nathan and Osk's Hematology 7th/643; NMS Medicine 5th/348*

***'Metallic heart valves' is the single best answer of exclusion.***

*Pathologically Prosthetic Heart valves are associated with macroangiopathic hemolytic anemias and not microangiopathic hemolytic anemias.*

*TTP, Antiphospholipid syndrome, vasculitis syndromes (including MPA) and mechanical heart valves may all give rise to hemolytic anemia due to red cell fragmentation. Most textbooks do not make a distinction between macroangiopathic and microangiopathic hemolytic syndromes and club all causes into the category of microangiopathic hemolytic anemias (including prosthetic valve hemolytic anemias)*

*However in strict terminology microangippathic hemolytic anemias result from cell fragmentation that occurs in the microcirculation.*

***Red cell fragmentation hemolytic anemias from prosthetic heart valves is strictly/pathologically a macroangiopathic hemolytic anemia and hence the single best answer of exclusion.***

**Mechanical Red Cell Fragmentation Syndromes**

| Macroangiopathic (large vessel) | Microangiopathic (small vessel) |
|---|---|
| Direct Red Cell trauma from an abnormal vascular surface.<br>• ***Prosthetic Heart Valves***$^{Q}$<br>• ***Synthetic vascular grafts***$^{Q}$<br>Large vessel disorders that may cause shearing of Erythrocytes<br>• *Cavernous Hemangioma* (Kasabach-Merritt syndrome) | Abnormalities in microcirculation that cause turbulent blood flow<br>• *DIC*<br>• *TTP*<br>• *HUS*<br>• *Vasculitis (Collagen Vascular Disorders)*<br>• *Malignant Hypertension/Eclampsia*<br>• *Disseminated carcinomatosis (Metastasis)*<br>• *Drugs / Radiation*<br>• *Antiphospholipid syndrome* |

**Antiphospholipid syndrome and microangiopathic hemolytic anemia**

*Microangiopathic hemolytic anemias has been found in association with the antiphospholipid antibody syndrome.*
*– NMS Medicine 5th/348*

Note:
***Both Harrison and CMDT classify Hemolysis in association with prosthetic heart valves as microangiopathic hemolytic anemia and hence 'none' would probably be the correct answer.***

**147. Answer is B (ITP):** Harrison 18th/883; *17th/658; CMDT 2007/533; 2009/442, 436; William's Hematology 6th/118*

*Idiopathic thrombocytopenic purpura is not a cause for microangiopathic hemolytic anemia.*

Note:

*Pathologically Prosthetic Heart valves are associated with macroangiopathic hemolytic anemias and not microangiopathic hemolytic anemias.However, most textbooks do not make a distinction between macroangiopathic and microangiopathic hemolytic syndromes and club all causes into the category of microangiopathic hemolytic anemias (including prosthetic valve hemolytic anemias)*

***Both Harrison and CMDT classify Hemolysis in association with prosthetic heart valves as microangiopathic hemolytic anemia and hence prosthetic valves is not excluded in this answer.***

**148. Answer is D (Microangipathic Hemolytic Anemia):**

*Shistocytes are fragmented red blood cells typically found in patients with microangiopathic hemolytic anemias.*

| *Schistocytes* |
|---|
| • Schistocytes are fragmented red blood cells, often showing a half-disk shape with two or three pointed extremities; they may be a small, irregular fragment.<br>• Schistocytes can be found in the Microangiopathic haemolytic anemias, thrombotic thrombocytopenic purpura (TTP), and haemolytic uremic syndrome (HUS).<br>• Schistocytes can also be seen in patients with disseminated intravascular coagulation.<br>• Other conditions in which Schistocytes can be seen include severe burns, March Hemoglobinuria, and Heart valve hemolysis. |

## Proxysmal Nocturnal Hemoglobinuria (PNH)

**149. Answer is B (Increased LAP scores):** *Harrison 18th/883, 884; 16th/ 616; 17th/ 660, 661; CMDT 2008/432; 2009/437*

*PNH is associated with a decreased Leukocyte Alkaline phosphase (LAP) score*

**PNH: Paroxysmal Nuctunal haemoglobinuria:** *Review*

**PNH** is an Acquired [Q] Intracarpuscular [Q] disorder, acquired at stem cell level [Q] by loss characterised by undue sensitivity of red blood cell's membrane to complement [Q]

**Common manifestations:** PNH : Three common manifestation

| **Hemolytic Anemia** | **Venous Thrombosis** | **Deficient Hematopoesis** |
|---|---|---|
| | | Probably due to defect at stem cell level |
| Because of increased activation of complement and complement mediated destruction → *Hemoglobinemia* [Q], *Hemoglobinuria* [Q], *Hemosiderinuria* [Q], ***Elevated LDH*** [Q] | Activation of complement indirectly stimulates platelet aggregation and hypercoagulability (thus thrombosis despite thrombocytopenia) | Pancytopenia/Aplastic anemia-H16th/ 618<br>- ↓ Granulocytes<br>- Thrombocytes (thrombocytopenia) |

**Why is it called Paroxysmal Nocturnal haemoglobinuria?**
**Basis** : *Acidification enhances activity of complement*

During night when one sleeps **(noctunal)** → Relative Hypoxia → Acidosis → Enhanced complement activity → Complement mediated destruction of red blood cells ← **Paroxysm** of **Haemoglobinuria** identified by passage of brown urine in morning.

Red Cell Membrane is **deficient in two factors** which result in increased activation of complement
1. **DAF** [Q] : Decay accelerating factor that activates decay of complements
2. MIRL CD 59 : inhibits membrane attack complex

**150. Answer is D (Massive splenomegaly):** *Harrison 18th/883, 884, 887; 17th/660, 661; Williams 7th/470; 'Blood' by Handin 2nd/326*

*PNH is usually not associated with a massive splenomegaly*

*'Splenomegaly is present in some patients with PNH, but the enlargement of spleen is usually quiet modest'.*
*– Williams Hematology 7th/470*

**Venous Thrombosis is a common manifestation/complication of PNH**

Venous Thrombosis

| Abdominal veins are the most common site of venous thrombosis in PNH | Cranial vein are the second most common site of venous thrombosis after abdominal veins-*'Blood' 2nd/326* |
|---|---|
| • ***Classic site of thrombosis is the Hepatic vein causing Budd Chiari syndrome.***<br>• Splenic veins, portal vein, mesenteric vessels, renal vein and inferior venacava may also be involved. | ***Frank Cerebral thrombosis is a grave complication of PNH.*** *– William's Hematology 7th/471* |

**PNH is associated with Pancytopenia** (Harrison 17th/663)
*PNH is a cause for Pancytopenia with a cellular marrow.*

**151. Answer is C (Increased alkaline phosphatase):** *See previous question*

*PNH is associated with a decreased leukocyte alkaline phosphate scape.*
Remember the following fact to answer several questions in our kind of examinations by the principle of exclusion:

| Conditions with decreased LAP scores | Conditions with increased LAP scores |
|---|---|
| 1. P.N.H. [Q] | 1. Polycythemia [Q] |
| 2. C.M.L. [Q] | 2. Leukemoid reaction [Q] |
| | 3. Infection [Q] |

**152. Answer is C (Paroxysmal Nocturnal haemoglobinuria):** Harrison 18th/p 883, 884 *Harrison16th/616; Harrison17th/660, 661; Robbins illustrated 5th/619, Robbins 7th/636*

***Paroxysmal nocturnal haemoglobinuria (PNH) results from an acquired somatic mutation on the pleuripotent stem cells. Hence all its clonal progeny i.e. red cells, white cells and platelets are affected*** *- Robbins 7th/ 636*

**Paroxysmal nocturnal haemoglobinuria**: is an acquired *clonal disease* that is associated with abnormality of complement regulation. *This defect affects the Pluripotent stem cells & the clonal progeny of these stem cells. Red cells, white cells & platelets thus all are affected.*

***Paroxysmal cold haemoglobinuria, Blackfan Diamond syndrome (pure red cell aplasia) and hemolytic anemias*** *characteristically involve the red cell lineage only.*

**153. Answer is A (Hypercellular marrow):** *Refer text below*

***PNH is associated with a normocellular or hypercellular marrow and not with a hypocellular marrow.***

*PNH is associated with an increased incidence of venous thrombosis and may lead to Budd-Chirai syndrome.*
*PNH is associated with decreased LAP scores.*

**154. Answer is C (Decreased LDH):** Harrison 18th/p 883, 884 *Harrison 16th/616; 17th/ 660, 661; Robbins illustrated 6th/681, Robbins 7th/ 630*

***Because of increased activation of complement and complement mediated destruction of RBC there occurs intravascular hemolysis and an elevated LDH is seen.***
Paroxysmal nocturnal haemoglobinuria may have thrombosis and thrombocytopenia both, as is depicted in the previous explanations.

**155. Answer is D (All of the above):** *Harrison 18th/p 883, 884; 17th/ed 660, 661 Wintrobe's Hematology 12th/1002;*

***PNH is associated with a deficiency of GPI anchored proteins including DAF and MIRL***
*PNH is associated with a deficiency of GPI Anchored proteins*
*DAF (CD55) and MIRL (CD59) are the most important GPI Anchored proteins that may be deficient in PNH.*
***Since option 'D' allows us to select all the above options and we are not forced to select one single best protein 'Option D' becomes the answer of choice.***

**Glycosyl phosphatidylinositol (GPI) anchored proteins and PNH**

- PNH is primarily associated with a deficiency of GPI anchored proteins on hemotopoetic cells
  ***All proteins that are deficient in PNH are GPI Anchored and all GPI anchored proteins that are expressed by hematopoietic cells are deficient in PNH'*** *– Wintrobe's*
- The most important GPI anchored proteins that are causally related to PNH are the complement regulatory proteins that result in abnormal susceptibility of erythrocytes to complement mediated lysis.

| GPI Anchored complement regulatory proteins |
|---|
| *Decay accelerating factor (DAF – CD 55)* |
| *Membrane Inhibitor of Reactive Lysis (MIRL – CD59)* |

- However several other GPI anchored proteins may be deficient in PNH and currently the list of proteins deficient in PNH numbers more than 20

| GPI Anchored Proteins Deficient in PNH | |
|---|---|
| • Leukocyte alkaline phosphatase | • CD66b (formerly CD67) |
| • Acetylcholinesterase | • CD66c |
| • Decay accelerating factor (DAF, CD55) | • p50-80 |
| • Membrane inhibitor of reactivity lysis (MIRL, CD59) | • CD24 |
| • FcγRIIIb (CD16b) | • CD48 |
| • Lymphocyte function-associated antigen 3 (LFA-3, CD58) | • Thy-1 (CD90) |
| • Endotoxin-binding protein (CD14) | • CD109 |
| • Campath 1 (CD52) | • CD157 |
| • 5'-ectonucleotidase (CD73) | • GP500 |
| • Urokinase plasminogen activator receptor (CD87) | • GP175 |
| • JMH-bearing protein (CD108) | • Folate receptor |
| | • Cellular prion protein |

**156. Answer is C (GPI Anchored Proteins):** Harrison 18th/p 883, 884 *Wintrobe's 12th/ 1002; Harrison's 17th/ed 660, 661*

*All of the proteins mentioned as options (DAF, MIRL and LFA) may be deficient in PNH and all of these proteins are GPI anchored proteins.* ***Since we have to chose a single best answer amongst the options provided, GPI Anchored proteins becomes the answer of choice.***

*'All proteins that are deficient in PNH are GPI Anchored and all GPI – Anchored proteins that are expressed by hematopoetic cells are deficient in PNH' - Wintrobe's Hematology*

***All proteins deficient in PNH are GPI anchored proteins and hence GPI anchored proteins is the single best answer of choice***

**157. Answer is B (Complements):** Harrison 18th/p 884 *Harrison 16th / 616; Harrison 17th/ 661*

***HAM test is based upon susceptibility of RBC's to complement mediated lysis in patients with PNH.***

*HAM test is used for the diagnosis of PNH (Paroxysmal Nocturnal Haemoglobinuria). HAM test (Acidified serum lysis test) demonstrates lysis of RBC after activation of complement by acid.* ***In acidified serum complement is activated by the alternate pathway.*** *In patients with PNH, RBC are unusually susceptible to complement, and undergo lysis when incubated with acidified fresh serum.*

**Diagnosis of PNH**

| Flow cytometry | Demonstration of Lysis of RBC after complement activation |
|---|---|
| ▪ *Test of Choice*<br>▪ Analyses GPI - Linked proteins<br>- CD 59 (MIRL)<br>- DAF (CD55)<br>▪ These proteins block activation of complement on cell surface.<br>Their absence accounts for sensitivity of RBC to complement lysis | ▪ Ham Test (complement activation by acid)<br>▪ Sucrose lysis test (complement activation by reduction in ionic strength) |

**158. Answer is A (Flow cytometry):** *Harrison's 18th/884;*

***Gold standard diagnostic test for PNH is the flow cytometric quantitation of GPI-linked proteins.***

*Flow cytometry is used to detect CD 59 (MIRL), a glycoprotein, and CD 55 (DAF) in regulation of complement action. The definitive diagnosis of PNH is based on demonstration that a substantial proportion of the patient's red blood cells have an increased susceptibility to complement due to deficiency of CD 59 (MIRL) and CD 55 (DAF) on their surface that normally protect the red cells from activated Complement. Flow cytometry is the gold standard test to detect CD 59 and CD 55. Absence or reduced expression of both CD 59 and CD 55 on PNH RBCs is diagnostic.*

## Aplastic Anemia and Myelodysplastic Syndrome

### Aplastic Anemia and Pancytopenia

**159. Answer is D (Cold haemoglobinuria):** Harrison 18th/p 888; table 107.2 *Harrison 16th/ 618; 17th/ 663; table 1022; Chandrasoma Taylor 3rd/ 381*

***Paroxysmal Cold Hemoglobinuria is a form of immune mediated hemolytic anemia and is not a form of aplastic anemia.***

*Pregnancy, PNH and hepatitis have all been mentioned as causes of Aplastic anemia.*

**Classification Of Aplastic Anemia And Cytopenias :**

| *Acquired* Aplastic Anemia | *Inherited* Aplastic Anemia |
|---|---|
| **Radiation** | Fanconi's anemia |
| **Drugs and chemicals** | Dyskeratosis congenita |
| Regular effects | Shwachman-Diamond syndrome |
| Idiosyncratic reactions | Reticular dysgenesis |
| **Viruses** | Amegakaryocytic thrombocytopenia |
| Epstein-Barr virus (infectious mononucleosis) | Familial aplastic anemias |
| **Hepatitis** (non-A, non-B, non-C hepatitis) | Preleukemia (monosomy 7, etc.) |
| Parvovirus B19 (transient aplastic crisis. PRCA) | Nonhematologic syndrome |
| HIV-1 (AIDS) | (Down's Dubowitz, Seckel) |
| **Immune diseases** | |
| Eosinophilic fasciitis | |
| Hypoi-immunophilic globulinemia | |
| Thymoma/thymic carcinoma | |
| Graft-versus-host disease in Immunodeficiency | |
| **Paroxysmal nocturnal hemoglobinuria** | |
| **Pregnancy** | |
| **Idiopathic** | |



**160. Answer is C (Hepatitis A):** Harrison 18th/p 887, 888 *Harrison 17th/663, 664*

***Aplastic anemia is associated with Non-A, Non-B, Non-C, Hepatitis and not with Hepatitis A***

*Parvovirus B19, HIV-1, Chloramphenicol and PNH are all associated with Aplastic anemia.*

**161. Answer is A (PNH) :** Harrison 18th/p 883, table 107.1 *Harrison 16th / 617; 17th / 663; table 102-1*

***Amongst the options provided PNH is the single best answer of choice.***

Differential diagnosis of Pancytopenia

| **Pancytopenia with Hypocellular Bone Marrow** |
|---|
| Acquired aplastic anemia |
| Constitutional aplastic anemia |
| (Fanconi's anemia, dyskeratosis congenita) |
| Some myelodysplastic syndromes |
| Rare aleukemic leukemia (AML) |
| Some acute lymphoid leukemia |
| Some lymphomas of bone marrow |

| **Hypocellular bone marrow ± Cytopenia** |
|---|
| Q fever |
| Legionnaires' disease |
| Anorexia nervosa, starvation |
| Mycobacteria |

| **Pancytopenia with Cellular Bone Marrow** | |
|---|---|
| *Primary bone marrow diseases* | *Secondary to systemic diseases* |
| *Myelodysplasia syndromes* | Systemic lupus erythematosus |
| ***Paroxysmal nocturnal hemoglobinuria*** | Hypersplenism |
| *Myelofibrosis* | ***$B_{12}$, folate deficiency (Megaloblastic Anemia)*** |
| Some aleukemic leukemia | Overwhelming infection |
| Myelophthisis | Alcohol |
| Bone marrow lymphoma | Brucellosis |
| Hairy cell leukemia | Sarcoidosis |
| | Tuberculosis |
| | Leishmaniasis |

**162. Answer is C (Dyskeratosis Congenita ):** *Harrison's 18th/887*

***Dyskeratosis congenita (constitutional aplastic anemia) is associated with Pancytopenia and a Hypocellular bone marrow***

*Myelodysplasia, PNH and Sarcoidosis may all be associated with Pancytopenia and a cellular bone marrow*

**163. Answer is A** *(Fanconi's Anemia): Harrison 18th/887*

***Constitutional Aplastic Anemias like Fanconi's Anemia are associated with a Hypoplastic Marrow***

*Myelofibrosis, Paroxysmal Nocturnal Hemoglobinuria (PNH) and Hypersplenism are all associated with a cellular marrow.*

**164. Answer is Both B and A (B > A):** Harrison 18th/p 884, 887 *Harrison 16th / 616; Harrison17th/661, 663; Robbins 7th / 638; CMDT 2006 / 491; CMDT 2009/437; Read previous question*

***According to the reference table from Harrison, both Megaloblastic anemia and PHN may present with pancytopenia and cellular bone marrow. Bone marrow in megalobastic anemia is almost always hypercellular while in cases of PHN this may be normocelllar, hypercellular or hypocellular. Thus megalobastic anemia is the single best answer of choice here.***

*Note that a 'Cellular bone marrow' is not synonymous with a 'Hypercellular' marrow. Even a 'Normocellular' marrow is classified as a 'Cellular' marrow. The question is specific for hypercellular marrow.*

| PNH | Megaloblastic anemia |
|---|---|
| *'Bone marrow may appear* ***normocellular*** *' (H16th/ 616) (ie. cellular but not necessarily hypercellular)*<br><br>*'Bone marrow morphology is variable and may show either generalized* ***hypoplasia*** *or erythroid* ***hyperplasia'*** *– CMDT 2006 / 49)*<br><br>***It may thus be hypocellular, normocellular or hypercellular*** | ***'Bone marrow is hypercellular*** *with a decrease myeloid / erythroid ratio and abundant stainable iron' – Harrison 16th / 606*<br><br>***'Marrow is usually markedly hypercellular*** *due to increase number of all types of myeloid precursors which may completely replace the fatty marrow' – Robbin's 7th / 638* |

**165. Answer is D (G6PD deficiency) :** Harrison 18th/p 887, 888 *Harrison 16th / 617, Harrison17th/663; (table 94-1) : Refer previous question*

***PNH, megaloblastic anemia, and Myelodysplasia may all present with pancytopenia and cellular marrow. G6PD deficiency is not associated with Pancytopenia and cellular marrow.***

**166. Answer is D (Dyskeratosis congenita):** Harrison 18th/p 887 *Harrisons 17th/663; Harrisons 16th/617*

***Dyskeratosis congenita is associated with Pancytopenia and a hypocellular marrow.***

**167. Answer is B (Dyskeratosis congenita):** Harrison 18th/ 887 *Harrisons 17th/663; Harrisons 16th/617*

***Dyskeratosis congenita is associated with Pancytopenia and a hypocellular marrow.***

**168. Answer is D (G-6PD Deficiency) :** Harrison 18th/ 887 *Harrisons 17th/663, Harrisons 16th/617*

***Glucose – 6 – PD Deficiency is not associated with Pancytopenia and a cellular marrow***
*Myelodysplasias, PNH and Megaloblastic anemia (Vit $B_{12}$, Folate deficiency) may present with Pancytopenia and a cellular marrow.*

**169. Answer is C (Aplastic anemia):** *Harrison 16th/ 617, Harrison17th/606; Robbins: Read text below.*

***Patient in question has anemia with pancytopenia and an enlarged spleen. Presence of an enlarged spleen makes aplastic anemia the least likely diagnosis.*** *All other conditions mentioned as options may present with both pancytopenia and splenomegaly.*

| Parameters | Normal | Patient in question | **Inference** |
|---|---|---|---|
| Hb | 12-18 g/dl | 8 gm/dl | *Anemia* |
| TLC | 4000-11000 / $mm^3$ | 3000/ $mm^3$ | *Granulocytopenia* |
| Platelet Count | 130,000-400000/$mm^3$ | 80,000/$mm^3$ | *Thrombocytopenia* |
| Spleen size | Not enlarged | Enlarged | *Splenomegaly* |

- **Aplastic anemia** may present with anemia and pancytopenia but not with an associated enlarged spleen.
  *'If splenomegaly is present the diagnosis of aplastic anemia is seriously questioned.' - Robbins*
- **Megaloblastic anemia:** Besides ineffective synthesis and increased hemolytic destruction of red blood cells, there also occurs premature destruction of granulocytes and platelet resulting in Leucopenia and thrombocytopenia – Pancytopenia (Robbins) An enlarged spleen may be associated.
- **Leukemia** : Aleukemic form of Acute Lymphocytic leukemia also explains both – pancytopenia and hepatosplenomegaly
- **A chronic disease** associated with splenomegaly also explains pancytopenia as a sequels to increased destruction as a manifestation of 'HYPERSPLENISM' (increased sequestration and destruction of cells in sinusoids of an enlarged spleen).

**170. Answer is A (Fanconi's Anemia)**

***Fanconi's Anemia is the most common congenital inherited Aplastic Anemia.***

**171. Answer is A (Autosomal dominant inheritance):** *Harrison's 17th/-665; API Textbook of Medicine 8th/828, 829; Wintrobe's Hematology 12th/1173, 1174*

***Fanconi's anemia is primarily inherited as an autosomal recessive disorder and not as an autosomal dominant disorder.***

**Fanconi's Anemia is inherited as an Autosomal Recessive / X- Linked disorder**

*There are currently 13 known subtypes of fanconi's Anemia. With the exception of one subtype (Subtype B) which is X-linked recessive, all other subtypes of Fanconi's anemia follow an* ***autosomal recessive pattern of inheritance.***

*- Wintrobe's Hematology*

**Fanconi's Anemia is associated with Pancytopenia and Hypocellular Bone Marrow**

*'Once pancytopenia develops, the bone marrow is hypocellular' – API Textbook of medicine*

Fanconi's anemia is associated with *progressive bone marrow failure*[Q]

*Pancytopenia*[Q] develops insidiously and presents in most cases between the ages of 5 and 10 years

Bone marrow may show *normal cellularity initially*, however with progressive bone marrow failure pancytopenia develops and the bone marrow *becomes hypocellular.*

**Fanconi's anemia is usually normochronic, normocytic or macrocytic**

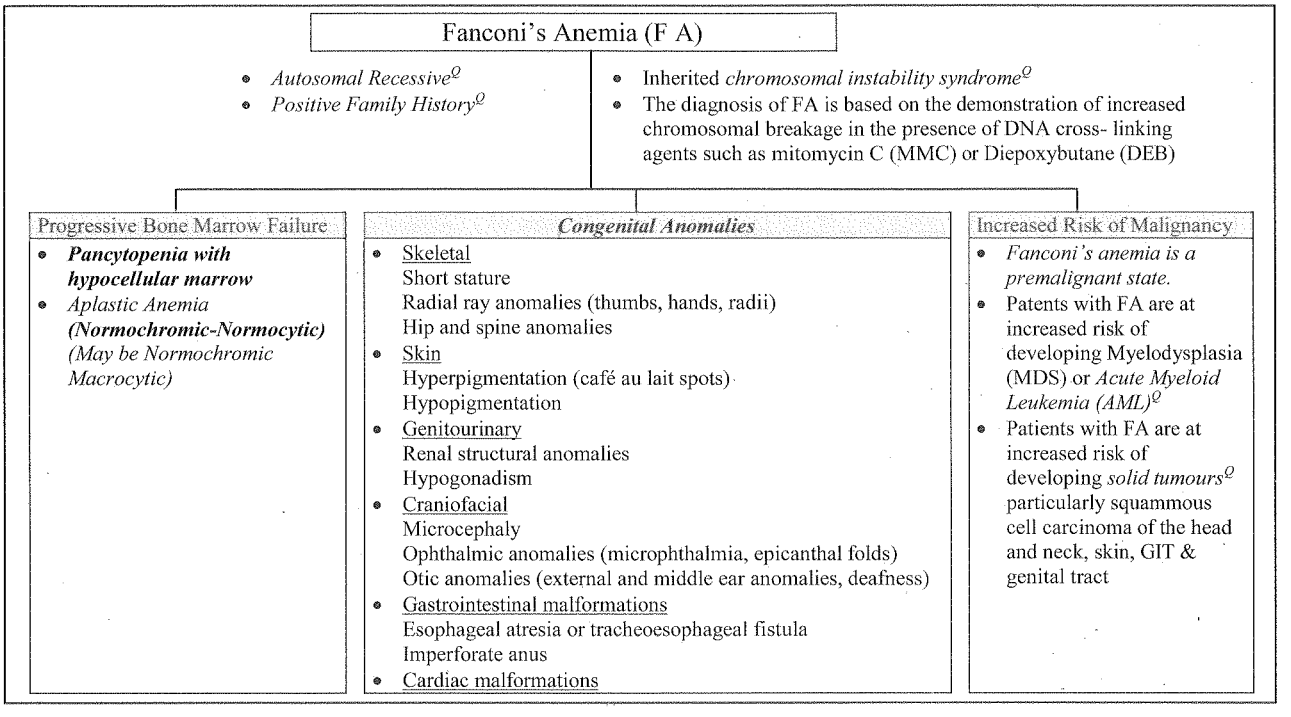
Fanconi's anemia is a form of inherited hypoproliferative aplastic anemia.

*'The hypoproliferative anemias are normochromic, normocytic or macrocytic and are charachterized by a low reticulocyte count' – Harrison's 17th/663*

| | |
|---|---|
| *Fanconi's Anemia* | *Normochromic- Normocytic > Normochromic – Macrocytic* |

**Fanconi's Anemia is associated with several congenital disorders**

*Fanconi's Anemia manifests as congenital developmental anomalies, progressive pancytopenia and an increased risk of malignancy- Harrison's 17th/665*




**172. Answer is D (Schwachman-Diamond syndrome):** *NORD Guide to Rare Disorders (Lippincott Williams & Wilkins, 2003)/417*

***The association of Pancreatic Exocrine Failure with Aplastic Anemia (Bone Marrow Failure) suggests a diagnosis of Schwachman-Diamond syndrome. Schwachman-Diamond syndrome is the second Most Common Cause of Pancreatic Exocrine Insufficiency after Cystic Fibrosis.***

***Shwachman–Diamond syndrome (SDS) or Shwachman–Bodian–Diamond syndrome is a rare autosomal recessive congenital disorder characterized by exocrine pancreatic insufficiency and bone marrow failure.*** *Other typically associated features include skeletal abnormalities and short stature.*

| Shwachman–Diamond syndrome (SDS) :Essentials of Diagnosis |
|---|
| • Pancreatic Exocrine Insufficiency<br>• Bone Marrow Failure (Intermittent or Persistent Cytopenias, most commonly Neutropenia)<br>Skeletal Abnormalities and Short Stature are common associations |

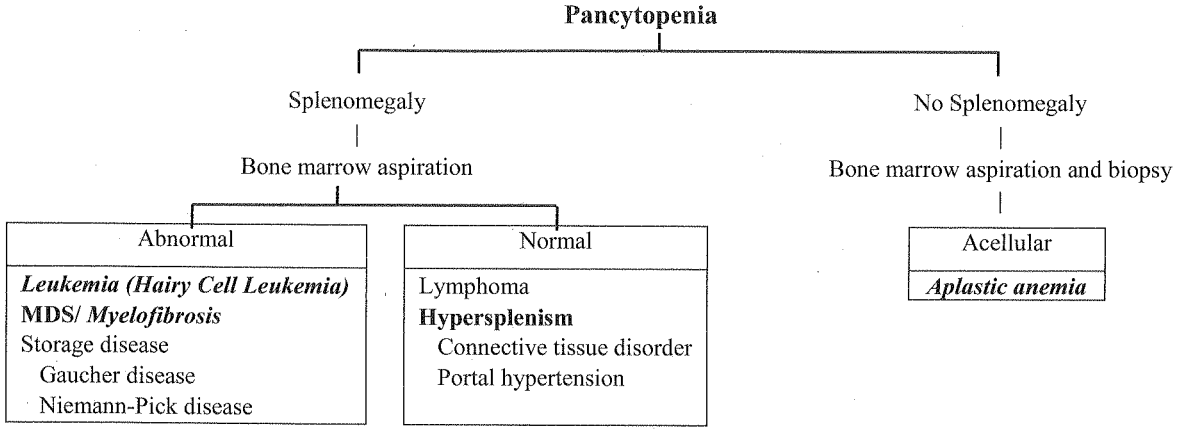
| | |
|---|---|
| *Autosomal Recessive Inherited Aplastic Anemia with Short Stature and Skeletal Abnormalities* ***with Pancreatic Exocrine Insufficiency*** | *Schwachman-Diamond syndrome* |
| *Autosomal Recessive Inherited Aplastic Anemia with Short Stature and Skeletal Abnormalities* ***without Pancreatic Exocrine Insufficiency*** | *Fanconi's Anemia* |

**173. Answer is A (Aplastic Anemia):** *Spiral Manual of Clinical Hematology (Lippincott Williams & Wilkins)3rd/ 64; Robbins 9th/ 424; Kelley's Essentials of Internal Medicine 2nd/431*

***Splenomegaly is typically absent in patients with aplastic anemia, and if present, the diagnosis of aplastic anemia should be questioned and search for another associated pathology be initiated.***

| Splenomegaly, Lymphadenopathy and Hepatomegaly in Aplastic Anemia |
|---|
| *The finding of splenomegaly or lymphadenopathy or hepatomegaly at presentation in patients with Aplastic Anemia is unusual and if present should cause one to question the diagnosis of aplastic anemia. Splenomegaly may develop later in the course of disease or after several blood transfusions* |

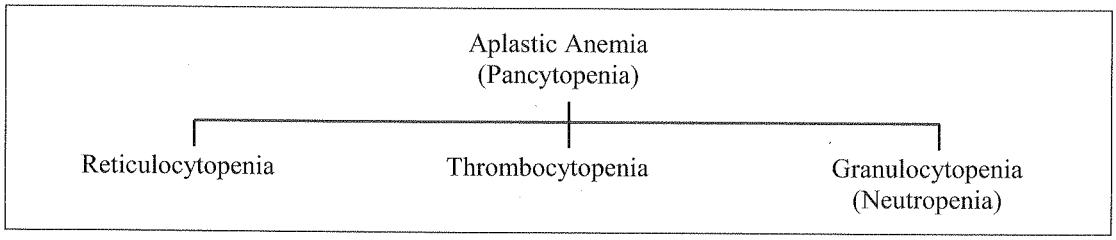
*Myelofibrosis and Hairy cell Leukemia are typically associated with Pancytopenia and Splenomegaly. Hypersplenism is also often associated with splenomegaly and Pancytopenia.*




**174. Answer is A (Splenomegaly):** *Robbins 7th/648*

***Splenomegaly is characteristically absent in Aplastic Anemia***

*'Splenomegaly is characteristically absent. If present, the diagnosis of aplastic anemia should be seriously questioned'*
*- Robbins*



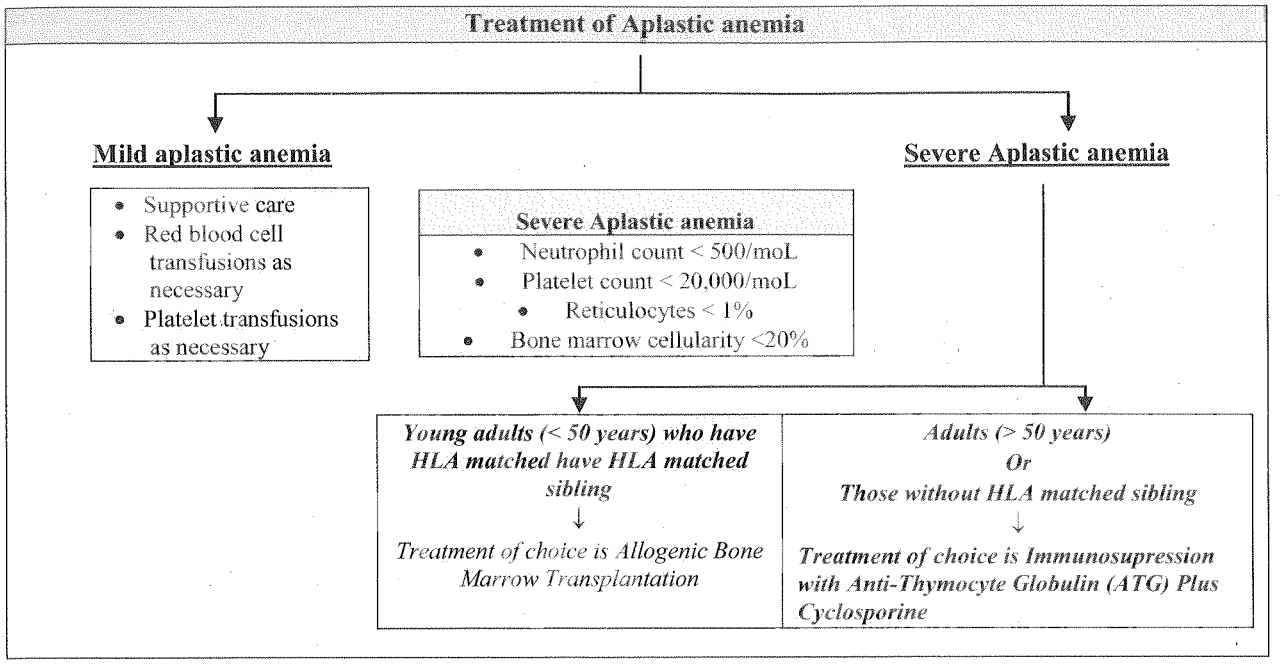

**175. Answer is A (Leukemia):** *Reference alongside; Robbins 7th/648, 652*

***The presence of Pancytopenia and 6% blasts in peripheral blood is enough to support the diagnosis of aleukemic leukemia.*** *Presence of splenomegaly eliminates aplastic anemia & ITP as the possibilities and hemolysis does not explain the low WBC and platelet count in the patient.*

- **Leukemia:** Although leukemia usually presents with an elevated WBC count the presence of Pancytopenia and 6% blasts in peripheral blood is enough to support the diagnosis of aleukemic leukemia. Some patients with aleukemic leukemia present with pancytopenia without circulating blasts. The diagnosis of leukemia in such patients should however be ideally made only once, a marrow blast count is done and it comes out to be > 30%.
- **Presence of splenomegaly eliminates aplastic anemia & ITP as the possibilities.**
  - Splenomegaly & Lymphadenopathy are extremely uncommon in **ITP** & their presence should lead one to consider other possible diagnosis – *Robbins 7th/652*
  - Splenomegaly is characteristically absent in **aplastic anemia** and if present the diagnosis of aplastic anemia should be seriously questioned - *Robbins 7th/648*
- **Hemolysis** does not explain the low WBC platelet count in the patient.

**176. Answer is A (Antithymocyte globulin followed by cyclosporine)**: *Harrison 18th/p 891, 892; Harrison 17th/666, 667; CMDT 2008/438;2009/443*

*'For adults over age 50 years or those without HLA matched siblings, the treatment of choice for severe Aplastic anemia is immunosupression with antithymocyte globulin (ATG) plus Cyclosporine' -CMDT 2006 / 498*




**177. Answer is D (Bone marrow transplantation):** Harrison 18th/p 891, 892; *Davidson 18th/ 769; Harrison 16th/ 621, Harrison 17th/ 666, 667*

*'Bone marrow transplantation is the best therapy for the young patient with a fully histocompatible sibling donor.'*
*– Harrisons 16th/ 621*

**The curative treatment for young (<20 year-old) patients with severe idiopathic aplastic anemia is allogenic bone marrow transplantation if there is an available donor.** Those with a compatible sibling donor should proceed to transplantation as soon as possible. – *Davidson.*

## Myelodysplastic Syndrome

**178. Answer is A (Myelodysplastic Syndrome (MDS):** Harrison 18th/p 455 *Harrisons 17th /361, Williams Hematology 7th/374, 823*

*'Based on the distinctive finding of ringed sideroblasts on the marrow iron stain, patients are diagnosed as having sideroblastic anemia – almost always reflecting myelodysplasia' – Harrisons*

***Ringed Sideroblasts are a charachteristic bone marrow finding in Myelodysplasia***

| What are Sideroblasts |
|---|
| Sideroblasts are Erythroblasts (Red blood cell precursors) that contain iron (ferritin) granules in their cytoplasm. The iron in these cells is normally located in the cytoplasm away from the nucleus (and stains positive for prussian blue).<br>In normal bone marrow sideroblasts constitute 20- 40% (approx 1/3rd) of red blood cell precursors |
| What are Ringed Sideroblasts |
| Ringed sideroblasts are abnormal sideroblasts seen in conditions with disturbed haem synthesis. In these cells iron accumulates within the mitochondria, surrounds the nucleus and does not progress into haemoglobin<br>Ringed sideroblasts are defined as Nucleated Red blood cells (Erythroblasts) containing five or more granules and encircling at least two – thirds of the nucleus.<br>Ring sidroblasts are pathological and their presence suggests a diagnosis of sideroblastic anemia whether congenital or acquired |

What are the conditions associated with Ringed Sideroblasts

***Ringed Sideroblasts may be seen in all causes of sideroblatic anemia whether Congenital or Acquired but are most often associated with Myelodysplastic syndromes***

| Causes of Sideroblastic Anemia (Ringed Sideroblasts in Bone Marrow) |
|---|
| 1. Hereditary Sideroblastic Anemia |
| 2. Acquired Sideroblastic Anemia |
| • Primary (Acquired) Sideroblastic Anemia ***(Myelodysplastic Syndromes)*** |
| • Secondary (Acquired) Sidroblastic Anemia : Secondary to |
| - Alcohol (Alcohol induced sidroblastic anemia)[Q] |
| - Lead (Lead induced sideroblastic anemia)[Q] |
| - Zinc (Zinc induced sidroblastic anemia)[Q] |
| - Drugs such as INH, pyrizinamide, cycloserine, chloramphenical etc. |
| - Other Myeloprolifirative disorders and Myelofibrosis |
| 3. Others (Rare) |
| - Thiamine responsive megaloblastic anemia |
| - Pearson's syndrome |
| - Hypothermia |
| - Certain Haemoglobinopathies |

**179. Answer is A (Myelodysplastic syndrome):** *Robbins & Cotran Pathologic Basis of Disease 11th/615*

***Pawn Ball Megakaryocytes are characteristic of Myelodysplastic Syndrome (MDS).***
*Pawn Ball Megakaryocytes are megakaryocytes with multiple, widely separated nuclei. Presence of Pawn Ball Megakaryocytes is a characteristic feature of megakaryocytic dysplasia in Myelodysplastic Syndrome.*

**180. Answer is D (> 50 years):** *Harrison 16th/624; API 7th/958*

***Idiopathic MDS is a disease of the elderly. The mean age of onset is 68 years.***

**Myelodysplastic Syndromes**

(Disease of the elderly with mean onset > 68 years)
Heterogenous group of haematological disorder

| Characterized by | Classified as |
|---|---|
| - Peripheral blood cytopenias<br>- Trilineage dysplastic changes<br>- Hypercellular bone marrow<br>- Propensity to undergo transformation into Acute Myeloid Leukaemia[Q]. | **The French American British Group has classified this disorder into 5 pathological entities**<br>- Refractory Anemia<br>- Refractory Anemia with ring sideroblasts<br>- Refractory Anemia with Excess blasts<br>- Refractory Anemia with Excess blasts in transformation<br>- Chronic Myelomonocytic Leukaemia |

**181. Answer is C (5q-):** *'Myelodysplastic Syndromes' by John Bennett (2002)300; Childhood Leukemias' 2nd/549*

***'Monosomy 7 is by far the most common cytogenetic abnormality in children (pediatric MDS) whereas 5q- is observed most frequently in adults'*** *– Myelodysplastic Syndromes by John Bennett (2002)/300*

| Cytogenetic Abnormalities in MDS: Facts to Remember |
|---|
| *Monosomy 7 is the most frequent cytogenetic abnormality in children.*[Q] |
| *Deletion 5q (5q-) is the most frequent cytogenetic abnormality in adults*[Q]. |
| *Trisomy 8 is the most frequent trisomy*[Q]. |

**Differences between Myelodysplastic Syndromes in children and Adults**
('Myelodysplastic Syndromes' 2002/300; 'Childhood Leukemias' 2nd/549)

| Feature | Children | Adults |
|---|---|---|
| • Frequency | Less common | More common |
| • Presence of sideroblasts | Uncommon (<2%) | More common (≈25%) |
| • Cytogenetic Abervations | | |
| -7/7q- | Most common (≈30%) | Less common (≈10%) |
| -5/5q- | Uncommon (≈1-2%) | Most common (≈20%) |

## Myeloproliferative Disorders

### General/Classification

**182. Answer is B (Acute myeloid leukemia):** *Harrison 18th/ 898;Harrison 15th/701, Harrison 16th/626; Harrison 17th/ 672*

*The myeloproliferative disorders are characterized pathophysiologically by clonal expression of a multipotent hematopoitic progenitor cell with the overproduction of one or more of the formed elements of Blood.* ***These disorders may transform into acute leukemia naturally or as a consequence of mutagenic treatment.***

**Myeloproliferative disorders classically include:**
- Polycythemia vera$^{Q}$
- Idiopathic myelofibrosis$^{Q}$
- Essential thrombocytosis$^{Q}$
- Chronic myeloid leukemia$^{Q}$

**183. Answer is B (Myelofibrosis):** *CMDT 2008/440; Harrison 18th/903*

Myelofibrosis may be associated with decreased white cell count and decreased platlet counts. Myelofibrosis is an established cause for panyctopenia with cellular marrow.

| Condition | WBCount | Hematocrit/ Red cell mass | Platelet count | Red cell morphology | Splenomegaly | Philadelphia chromosome |
|---|---|---|---|---|---|---|
| **CML** | ↑↑ | N | N or ↑ | N | ***Massive*** | Present |
| **Myelofibrosis** | N or ↓or ↑ | N or ↓ | ↓or N or ↑ | Abnormal | ***Massive*** | Absent |
| **Polycythemia** | N or ↑ | ↑ | N or ↑ | N | ***Moderate (Massive in late stages)*** | Absent |
| **Essential Thrombocytosis** | N or ↑ | N | ↑↑ | N | ***Mild*** | Absent |

**184. Answer is C (Essential Thrombocytosis (ET)):** *Refer previous question*

***Essential Thrombocytosis is not associated with massive splenomegaly.***

*'Physical Examination in Essential Thrombocytosis is generally unremarkable except* ***occassionally for mild splenomegaly****. Massive splenomegaly is indicative of another Myeloproliferative disorder in particular PV, PMF or CML'. – Harrison 18th/903*

*'Splenomegaly in Essential Thrombocytosis is seen in less than 30% of patients, and when palpable the spleen is usually not enlarged more than 4 cm below the left costal margin'. – 'Blood: Principles and Practice of Hematology' 2nd/414*

**185. Answer is C (Flow-cytometric analysis):** *Hematology in Clinical Practice 4th/222, 223; Williams 7th/28; Wintrobe's Atlas of Clinical Hematology 2006/217*

*Amongst the options provided flow cytometry analysis is the least commonly employed laboratory test for the evaluation of myeloproliferative syndromes and has only limited application and selective indications for its use.*

***Flow cytometry analysis is the single best answer of choice.***

***Complete blood picture including Red cell mass / Hematocrit estimation, Bone marrow aspirate studies and chromosomal Studies are key investigations for the differential diagnosis of chronic myeloproliferative disorders.***

Laboratory studies in the diagnosis of Myeloproliferative Syndromes

**Key laboratory Tests**

- **Blood counts and general blood picture evaluation including hematocrit / Red cell mass measurements and Red cell morphology**

| Condition | WBCount | Hematocrit/Red cell mass | Platelet count | Red cell morphology |
|---|---|---|---|---|
| CML | ↑↑ | N | N or ↑ | N |
| Myelofibrosis | N or ↓ or ↑ | N or ↓ | ↓ or N or ↑ | Abnormal |
| Polycythemia | N or ↑ | ↑ | N or ↑ | N |
| Essential Thrombocytosis | N or ↑ | N | ↑↑ | N |

*Abnormal Red cell morphology includes tear drop cells, schistocytes etc*
*An elevated red cell mass is important to distinguish polycythemia vera from other myeloproliferation disorders.*

- **Marrow Aspirate and Biopsy**
  These are considered *essential investigations* for the diagnosis of Myeloproliferative disorders.
  *Bone marrow aspirate (dry tap) is particularly important to distinguish myelofibrosis from other mycloproliferative disorders.*
- **Chromosomal studies (karyotyping) for cytogenetic abnormalities**
  Chromosomal *studies are important*, particularly to distinguish CML from other causes of myeloproliferative disorders
  CML philadelphia chromosome (9:22)

**Optimal/Other laboratory Tests**

**Flow cytometry**

Flow cytometry may be used in the assessment and diagnosis of myelodysplastic and myeloproliferative disorders, but this approach is controversial' – *William's hematology 7th/28*

'Flow cytometry may be used in cases of Myeloproliferative syndromes in cases in which cytogenetic studies fail to detect a clonal karyotype abnormality - *Wintrobe's atlas of hematology (2006)/217*

**186. Answer is C (Flow cytometry) :** Harrison 18th/p 898 *Read text below : Harrison 16th/626-631; Harrison 17th/ 672-676*

***All investigations other than flow cytometry mentioned in the options are indicated useful tests for diagnosis of respective myeloproliferative disorder.***

| Myeloproliferative disorder | Useful tests |
|---|---|
| Polycythemia vera | Elevated Red cell mass / with normal erythropoetin levels |
| Chronic myeloid leukemia | Chromosomal demonstration of Philadelphia chromosome or bcr /abl translocation |
| Chronic idiopathic Myelofibrosis | Dry tap on bone marrow aspiration alongwith characteristic peripheral blood picture |
| Essential thrombocytosis | Elevated Platelet count with cytogenetic evaluation to rule out CML or other myelodysplastic disorder |

## Polycythemia

**187. Answer is A (60% in Men; > 55% in Women):** *Harrison 18th/ 456; Hematology: Diagnosis and Treatment by Ronald Hoffman (Elsevier Health Sciences) 2013/*

***A haematocrit level greater than 60% in men or greater than 55% in women is associated with an elevated RBC mass (Polycythemia) in virtually every case.***

*'Hematocrit levels >50% in men or >45% in women may be abnormal. Hematocrit >60% in men and >55% in women are almost invariably associated with an increased red cell mass or Polycythemia' - Harrison*

*'A Hematocrit level greater than 60% in men or greater than 55% in women is associated with an elevated RBC mass (Polycythemia) in virtually every case' – Hoffman*

*Note : Hematocrit levels are not included in standard diagnostic criteria for diagnosis of Polycythemia Vera*

**188. Answer is D (High altitude):** *Harrison 18th/p 456, 898 Harrison 16th/336, 627; Harrison 17th/ 362, 363, 672*

***High altitude is associated with physiological increase in erythropoetin levels and leads to absolute polycythemia and not relative polycythemia.***

**Polycythemia**

| ***Spurious / Relative polycythemia*** | ***Absolute Polycythemia*** | |
|---|---|---|
| Actual 'red cell mass' remains constant, (erythrocytosis is apparent due to decrease in plasma volume – Geisbocks syndrome) | Red cell elevated | |
| ↓ | ***Primary*** | ***Secondary*** |
| Hypovolumia<br>Dehydration<br>(Dengue Haemorrhagic fever) | Polycythemia vera<br>Erythropoetin levels are normal | All causes for increase in erythropoetin levels |

***Relative erythrocytosis due to reduction in plasma volume alone is also known as stress or spurious erythrocytosis or 'Geisbock's syndrome'*** *– Harrison 16th/627*

**189. Answer is C (Spurious Polycythemia):** *Wintrobe's 12th/ 1263*

***Gaisbock syndrome refers to Spurious Polycythemia or Relative Erythrocytosis due to decreased plasma volume.***

**190. Answer is C (Red cell mass):** *Harrison 18th/p 899; Harrison 17th/ 672, 673*

*When confronted with an elevated Haemoglobin or Haematocrit the first step should be to determine whether this increase is due to absolute erythrocytosis or relative erythrocytosis.*

| Absolute erythrocytosis | Relative/ spurious erythrocytosis |
|---|---|
| True increase in red cell mass | Apparent increase in red cell mass due to reduction in plasma volume |

*'Red cell mass'* ***is the investigation of choice to determine such distinction****. Once 'red cell mass' determination confirms absolute erythrocytosis, a diagnosis of polycythemia vera can be established by demonstrating absence of elevation in serum erythropoetin levels.*

Increased hematocrit / Hb
↓
*Measure RBC Mass*

| Normal | Elevated |
|---|---|
| ↓ | ↓ |
| Relative erythrocytosis | Absolute erythrocytosis |
| ↓ | ↓ |
| Increase in hematocrit is due to decrease in plasma volume | *Measure erythropoetin levels* |

| Low | Elevated |
|---|---|
| ↓ | ↓ |
| Polycythemia vera | *Measure $O_2$ saturation* |

| Low | Normal |
|---|---|
| Hypoxic cause | Autonomous erythropoetin production |
| Pulmonary disease | 1. Smokers |
| Cardiac disease | 2. Tumors producing erythropoetin eg. Renal cell carcinoma |
| Other causes | |

**191. Answer is A (Cor pulmonale):** *Wintrobe's 12th/1263*

***Secondary polycythemia due to decreased tissue oxygenation may be seen in chronic corpulmonale.***
*Polycythemia may also be seen in association with cyanotic congenital heart diseases.*

**Secondary Polycythemia (Absolute Erythrocytosis)**

| **Physiologically Appropriate Polycythemia** (Secondary to decreased tissue oxygenation or hypoxic erythrocytosis) | **Physiologically inappropriate polycythemia** (Secondary to appropriate erythropoietin production or response) |
|---|---|
| • High-altitude erythrocytosis ***(Monge disease)***<br>• Pulmonary disease<br>- Chronic cor pulmonale<br>- Ayerza syndrome<br>• Cyanotic congenital heart disease<br>• Hypoventilation syndromes<br>- Primary alveolar hypoventilation<br>- Pickwickian syndrome, Ondine curse<br>- Positional desaturation<br>- Sleep apnea<br>• Abnormal hemoglobins<br>- Inherited<br>- Acquired: Drugs and chemicals, carboxyhemoglobin<br>• Familial polycythemia | • Tumors, cysts, hemangiomas, and so forth<br>• Androgen abuse<br>• Erythropoietin abuse<br>• Familial polycythemia |

**192. Answer is B (High Altitude Erythrocytosis):** *Wintrobe's 12th/ 1263*

***Monge's disease (Chronic Mountain Sickness) is also known as High Altitude Pathologic Erythrocytosis.***

| **Chronic Mountain Sickness; Monge's disease; (High Altitude Pathologic Erythrocytosis; High Altitude Excessive Polycythemia)** | |
|---|---|
| • Excessive Erythrocytosis (Hb≥19 /dL for females and ≥21/dL for males)<br>• Hypoxemia<br>• Pulmonary hypertension (in some cases)<br>• Right heart failure or Cor-Pulmonale (in severe cases)<br>• Recovery on descent to low altitude | *Chronic Mountain Sickness is a clinical syndrome that occurs in natives or long-life residents above 2500m.* Headache, dizziness and fatigue are typical initial presenting symptoms |

**193. Answer is B (Arterial oxygen tension < 90% on room air):** Harrison 18th/p 899 *Harrison 17th/672, 363*

***Arterial oxygen tension < 90% on room air indicate a secondary cause of polycythemia from either heart or lung disease***

***Primary polycythemia (Polycythemia vera) is characteristically associated with a normal arterial oxygen saturation >92% on room air.***

*Both primary and secondary polycythemia will have an elevated red cell mass.*

*Pruritis and Hypertension are consequences of increased red cell mass and the resultant hyperviscocity, and may hence be seen in both forms of polycythemia.*

A summary of significant differences between Polycythemia Vera and Other Types of Polycythemia

| **Findings** | **Polycythemia vera** | **Secondary polycythemia** |
|---|---|---|
| *Red cell mass* | *Increased* | *Increased* |
| Erythropoietin | Decreased or absent | Normal or increased |
| ***Arterial oxygen saturation*** | ***Normal*** | ***Decreased or normal*** |
| Erythrocyte sedimentation rate | Decreased | Normal |
| Leukocyte alkaline phosphate stain | Increased | Normal |
| Vitamin B12 binding capacity | Increased | Normal |
| Total leukocytes | Increased (Leukocytosis) | Normal |
| Total Platelets | Increased (Thrombocytosis) | Normal |
| Basophil count | Increased | Normal |
| Blood histamine | Increased | Normal |
| Serum iron | Decreased | Normal or increased |
| Splenomegaly | Present | Absent |
| Marrow | Panhyperplasia | Erythroid hyperplasia |

**194. Answer is D (Pancreatic carcinoma) :** *Harrison 16th / 569, 627; Harrison 17th/ 621, 673*

*Ectopic production of erythropoietin by cancer cells cause most paraneoplastic erythrocytosis. Cancers typically associated with this syndrome include Renal cancer, Hepatocarcinoma and cerebellar hemangioblastomas.*

| Syndrome | Protein | Cancers typically associated with syndrome |
|---|---|---|
| *Erythrocytosis Paraneoplastic syndrome* | ***Erythropoetin*** | • ***Renal cancers*** <br> • ***Hepatocarcinoma*** <br> • ***Cerebellar hemangioblastoma*** |

**Tumours associated with Erythrocytosis :** *Harrison 16th / 627*

- ***Hypernephroma***
- ***Hepatoma***
- ***Cerebellar Hemangiblastoma***
- Adrenal adenoma
- Pheochromocytoma
- Meningioma
- Uterine fibromyoma

**195. Answer is D (Spontaneous severe infection):** *Harrison 18th/p 898, 899; Harrison 17th/ 672, 673*

*All options other than spontaneous severe infections have been mentioned as common associations with Polycythemia vera.*

**Polycythemia vera:**

Polycythemia is a disorder of multipotent haematopoetic progeniter cells, characterised by :
- overproduction of phenotypically normal red cells, granulocytes and platelets.
- In absence of recognizable physiological stimulus.

**Polycythemia Vera**

**Increase In Blood Viscosity**
- Neurological symptoms ♀
  - vertigo, tinnitus
  - headache
  - visual disturbance
- Systolic Hypertension ♀
- Venous or arterial thrombosis ♀
- Digital ischaemia
- Easy bruising, epistaxis or gastrointestinal haemorrhage.

**Increased Turnover of RBC, Leucocytes, platelets**
↓
increased uric acid ♀
increased histamine release
↓
- Peptic ulcer disease ♀
- Pruritis ♀

**Myeloproliferative Syndrome** ♀
May transform into acute Leukemia naturally or as a consequence of mutagenic treatment.

Note: Polycythemia is associated with an increased risk of both thrombosis and bleeding.

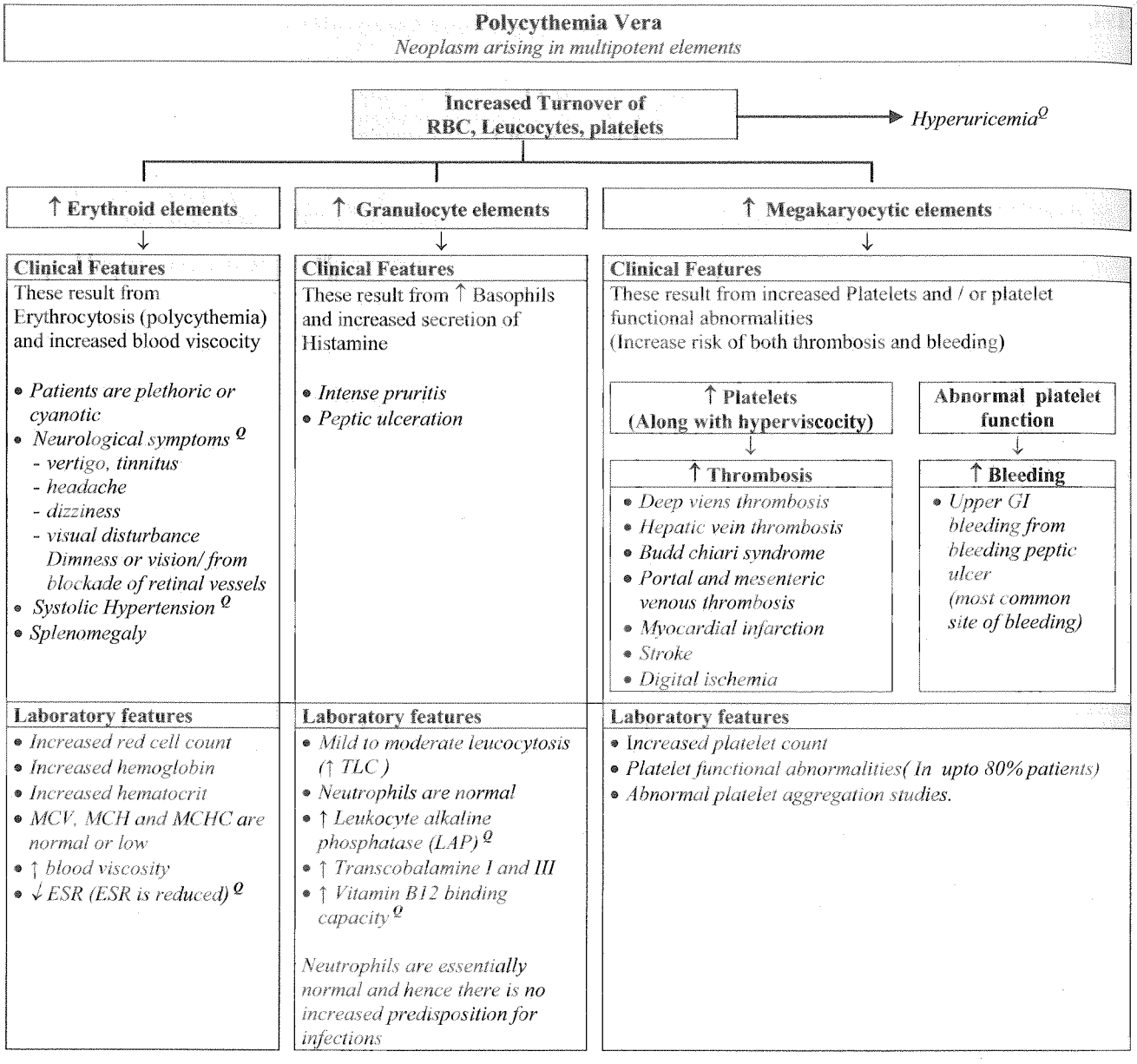
**196. Answer is D (Increased Infection):** Harrison 18th/p 899, 900 *Harrison 17th/672, 673; Harrison 16th/627, 628; Harrison 15th/702*

*Polycythemia vera is not associated with an increased predisposition to infections.*

**ESR levels are characteristically normal or reduced**

*'ESR' is characteristically low or normal. If this is abnormal another diagnosis or a complication shiuld be considered'*
*- Diagnostic Hematology*

**Polycythemia vera is associated with an increased incidence of both thrombosis and bleeding**
*Both arterial and venous thrombosis may be seen in Polycythemia vera.*
*Paradoxically patients may show a tendency of bleeding and bruising, mainly due to platelet of dysfunction.*




**197. Answer is A (Thrombocytopenia):** Harrison 18th/p 899, 900 *Harrison 15th/ 702; Harrison 16th/627; Harrison 17th/ 672, 673*

***Polycythemia vera is associated with thrombocytosis and not thrombocytopenia***

**Polycythemia vera is associated with thrombocytosis and not thrombocytopenia**

**Polycythemia Vera** is an acquired myeloproliferative disorder that is characterised by *overproduction* of *three hematopoitic cell lines* with *predominant elevation in RBC's*.
Thus there is overproduction of granulocytes, red cells and platelets. Overproduction of platelets results in thrombocytosis. Thrombocytopenia is not seen.

**Polycythemia vera is associated with an increased incidence of both thrombosis and bleeding**
*Both arterial and venous thrombosis may be seen in Polycythemia vera.*
*Paradoxically patients may show a tendency of bleeding and bruising, mainly due to platelet of dysfunction.*

**Transient visual loss may be seen in polycythemia vera as a manifestation of associated hyperviscosity syndrome.**

**198. Answer is B (Decreased LAP Score):** *Harrison 15th/ 702, 16th/ 627, 628; Harrison 17th/ 673; CMDT 2008/440; 2009/446*

***Leucocyte alkaline phosphatase is increased in polycythemia vera***

**Characteristic features associated of polycythemia vera**

- *Elevated Red Cell Mass/ haematocrit* (polycythemia) Q
- *Normal arterial oxygen saturation* Q (a low oxygen saturation would be a physiological stimulus)
- *Plasma erythropoetin levels < 4 mu/ml* (normal range : 4-26 mu/ml) (not increased) Q
- *Increased Leucocyte alkaline phosphatase* Q
- *Increased uric acid* Q-
- *Increased serum vitamin B12 or vitamin B12 binding capacity* Q
- *Massive splenomegaly or in the absence of splenomegaly leucocytosis & thrombocytosis* Q
- *No increase in ESR* Q

**Memo :**

LAP score is decreased in
- CML
- PNH

**199. Answer is A (Presence of JAK-2 mutation):** Harrison 18th/p 898, 899 *Wintrobe's Clinical Hematoogy 12th/ 1991, 1992; The Merck Manual: chapter 141/ section 11; William's Hematology 7th/790; Harrison's 17th/ed 672, 673*

***Presence of JAK-2 mutation is a Major criterion for diagnosis of polycythemia Vera according to the proposed new WHO criteria for the diagnosis of Polycythemia Vera.***

*Low Erythropoetin levels, Thrombocytosis and increased LAP scores are all minor criteria for diagnosis of polycythemia Vera.*

**JAK-2 Mutation and Polycythemia Vera**

- JAK-2 is a member of an evolutionarily well conserved, non receptor *tyrosine kinase family* and serves as the cognate *tyrosine kinase* for the erythropoietin receptors
- A mutation in the tyrosine kinase JAK-2 appears to have a central role in the pathogenesis of PV by causing constitutive activation of the kinase
- The presence of JAK -2 mutation thus allows for the exclusion of a reactive erythrocytosis. The 2001 WHO criteria for diagnosis of PV were however developed prior to the discovery of this important mutation and hence revised WHO criteria have been developed that include presence of JAK-2 mutation as a major criterion for diagnosis of PV

**Note**
*Although presence of JAK-2 mutation is a major criterion for diagnosis of PV, the presence of JAK-2 mutation alone is not diagnostic of PV. JAK-2 mutations may also be seen in other myeloproliferative disorders such as Essential Thrombocytosis (ET) and Chronic Idiopathic Myelofibrosis (CIMF).*

**Various major and minor criteria used for the diagnosis of polycythemia vera in various classification systems**
*(WHO criteria (revised and old )/ Polycythemia vera study group criteria)*

| Major | Minor |
|---|---|
| • ***JAK2 V617F mutation*** | • ***Thrombocytosis*** *(> 400 × 10⁹/L)* |
| • *Hemoglobin >18.5 g/dL in men, 16.5 g/dL in women* | • ***Leucocytosis*** *(WBC > 12 × 10⁹/L)* |
| • *Increased red blood cell mass* | • ***Increased leukocyte alkaline phosphatase*** *(LAP > 100U)* |
| • *Splenomegaly* | • *Increased serum B12/binders (B12 > 900 pg/ml; unbound B12 binding capacity > 2200 pg/ml)* |
| • *Clonal genetic abnormality other than Philadelphia chromosome or BCR/ABL in marrow* | • *Low serum erythroprotein levels.* |
| • *Endogenous erythroid colony formation in vitro* | • *Panmyelosis with prominent erythoid and megakaryocytic hyperplasia on bone marrow biopsy.* |
| • *Normal arterial O2 saturation (>92%)* | |

**Revised WHO criteria (Proposed) for the diagnosis of Polycythemia vera**

| Revised WHO criteria (Proposed) for the diagnosis of Polycythemia vera |
|---|
| **Major Criteria** |
| • Hemoglobin > 18.5 g/dl in men, > 16.5 g/dl in women or evidenced on increased red cell volume |
| • ***Presence of JAK2 mutation*** |
| **Minor Criteria** |
| • Hypercellular bone marrow biopsy with panmyelosis with prominent erythroid, granulocytic, and megakaryocytic hyperplasia |
| • Low serum erythropoietin level |
| • Endogenous erythroid colony formation in vitro. |

**WHO Criteria for the diagnosis of Plycythemia Vera (Prior to the proposed new criterion)**

| WHO Criteria *(Previous)* for the diagnosis of Plycythemia vera |
|---|
| **Major Criteria** |
| • Red blood cell mas > 25% above mean normal predicted value, or Hb > 18.5 g/dl in men, 16.5 g/dl in women. |
| • Splenomegaly on palpation |
| • Clonal genetic abnormality other than Philadelphia chromosome or BCR/ABL in marrow. |
| • Endogenous erythroid colony formation in vitro |
| **Minor Criteria** |
| • Thrombocytosis > 400 × $10^9$/L |
| • WBC > 12 × $10^9$/L |
| • Panmyelosis with prominent erythroid and megakaryocytic hyperplasia on bone marrow biopsy. |
| • Low serum erythropoietin levels. |

**200. Answer is B (Increased erythropoieten level):** Harrison 18th/p 899 *Harrison 16th/ 627; Harrison 17th/ 672, 673*

*Polycythemia vera is characterized by an increase in red cell mass without any increase in level of erythropoietin. In fact erythropoietin level is decreased due to feedback by increased erythrocytes.*
*The plasma erythropoetin level is a useful diagnostic test in patients with isolated erythrocytosis, because an elevated level excludes polycythemia vera as the cause for erythrocytosis.*

**201. Answer is C (Cerebellar haemangioblastoma):** *Harrison 18th/899; 14th/ 680; 15th/ 702, 16th/ 627; Harrison 17th/ 673*

| Tumors associated with polycythemia vera are : | |
|---|---|
| • Hypernephroma | • ***Cerebellar Haemangioblastoma*** |
| • Hepatoma | • Uterine fibromyoma |
| • Adrenal adenoma | • Meningioma |
| • Pheochromocytoma | |

## Myelofibrosis

**202. Answer is D (Myelofibrosis):** Harrison 18th/p 901 *Harrison 16th/628,629; 17th/674,675; CMDT 08,442,443; 2009/448; Chandrasoma Taylor 3rd/ 421*

***Presence of dry tap (unsuccessful aspiration), tear drop cells and splenomegaly all suggest a diagnosis of myelofibrosis.***

**Myelofibrosis:** *Review*

***Extensive fibrosis of bone marrow as part of myelofibrotic / proliferative disorder***

*Unsuccessful ♀ aspiration of bone marrow – **Dry Tap***

| Ineffective erythropoiesis in bone marrow | Compensatory haematopoesis at extramedullary sites ♀ | |
|---|---|---|
| • *Leukoerythroblastic ♀ picture*<br>- Immature Leucocytes<br>- Immature RBC's (nucleated)<br>• *Abnormal large platelets ♀ (dysplastic megakaryocytes)* | ***Tear drop ♀*** poikilocytes (red blood cells produced at these abnormal sites are often have abnormal and variable shapes) | ***Spleen is enlarged ♀*** (as it is the principal site of extramedullary haematopoesis.) |

**203. Answer is C (Myelofibrosis):** Harrison 18th/p 901 *Harrison 16th/ 628, 629; Harrison 17th/ 674, 675 Chandrasoma Taylor 3rd/ 421*

*Presence of a dry tap from the marrow and tear drop cells in the peripheral smear suggests the diagnosis of myelofibrosis.*

- Because of the fibrotic nature of this disorder, bone marrow aspiration is generally unsuccessful and yields a '***dry tap***'.
- ***Tear drop cells*** are suggestive of extra medullary haematopoesis as in spleen.

**Most characteristic are the Laboratory findings and the *triad of*** Q

a. Tear drop poikilocytes Q
b. Leukoerythroblastic blood i.e. immature leukocytes and nucleated (immature) RBC's Q
c. Giant abnormal platelets Q

*Biopsy of bone marrow to detect reticular or collagen fibrosis is essential for diagnosis.* Q

**204. Answer is D (Thalassemia):** Harrison 18th/p 896, 901, 902 *Harrison 15th/ 700, 701, 703; Harrison 16th/ 626, 629; Harrison 17th/ 669, 670, 674, 675*

*Leukoerythroblastosis is usually accompanied by fibrosis of the bone marrow and may be seen in all conditions associated with primary or secondary myelofibrosis / myelophthesis. Amongst the options provided all conditions other than thalassemia may produce fibrosis in the marrow and may produce a leukoerythroblastic picture.*

**Leucoerythroblastosis:**

- Refers to the presence of a variable number of immature erythroid and myeloid cells in circulation.
- This picture is indicative of ineffective erythropoesis in the normal marrow and extension of haematopoesis into extramedullary sites such as spleen, liver and Lymphnodes.
- It is usually accompanied by fibrosis of the bone marrow.

*Causes include:*

**Primary Myelofibrosis**

**Secondary myelofibrosis or Myelophthesis**

- Infections:
  - T.B. fungal, HIV etc.
- Tumors:
  - Metastastic carcinomas
  - Lymphomas e.g. Hodgkins
  - Leukaemias e.g. CML, AML, Hairy cell.
  - Plasma cell disorders :
  - Multiple Myeloma
  - Polycythemia vera
- Lipid deposition:
  - Gaucher's disease
- Radiation therapy

## Essential Thrombocytosis

**205. Answer is C or D (Anagrelide or Interferon Alpha) :** Harrison 18th/p 904 *CMDT 2008/442; 2009/437; Harrison 16th/630, 631; 17th/ 676, 677*

*This is a case of essential thrombocytosis. Interferon α and Anagrelide are the recommended treatment modalities for reducing platelet count in this disorder.*

*Previous editions of Harrisons and most other texts recommend hydroxyurea as the standard modality of treatment, but in view of the text mentioned in Harrisons 16th, hydroxyurea cannot be picked as the answer.*

**Essential thrombocytosis**

**(essential thrombocythaemia; idiopathic thrombocytosis; hemorrhagic thrombocythaemia)**

Essential thrombocytosis is a myeloproliferative disorder characterized by overproduction of platelets without a definable cause.

| Clinical features | Laboratory Diagnostic features |
|---|---|
| Symptoms<br>• Haemorrhagic tendencies : Easy bruising ♀<br>• Thrombotic tendencies : Microvascular occlusions<br>- Erythromelalgia<br>- Migraine (headache)<br>- Transient ischemic attacks<br>Signs<br>• Splenomegaly : usually mild/moderate *massive splenomegaly is more characteristic of other myeloproliferative disorders.* | • Elevated platelet count is hallmark (often $>1000\times10^3/\mu L$)<br>• Haematocrit and RBC morphology normal<br>• WBC count is mildly elevated/normal (mild neutrophillic leucocytosis)<br>• LAP is normal or elevated<br>• Philadelphia chromosome is absent |

| Management in asymptomatic patient | Management in symptomatic patient |
|---|---|
| Elevated platelet count in asymptomatic patient<br>• No therapy is recommended because agents used in treatment place the patient at risk of developing acute leukemia<br>↓<br>Therapy with risk of acute leukemia<br>• Radioactive phosphorus<br>• Hydroxyuria<br>• Alkylating agents | Elevated platelet count in symptomatic patients<br>• Symptoms must be clearly identified to be a consequence of elevated platelet count<br>↓<br>Platelet reduction<br>• IFN a<br>• Anagrelide<br>• Hydroxyurea: *should be considered only if the above agents are not effective or tolerable*<br>*.- Harrison* |

**206. Answer is B (Essential thrombocythemia) :** *CMDT 2008 / 441, 442; 2009/447; Robbins 7th / 700*

*Since all Myeloproliferative disorders can be associated with Thrombocytosis, Essential Thrombocytosis is a diagnosis of exclusion. The absence of an elevated Haemoglobin makes Polycythemia unlikely (Polycythemia is associated with increased Hb) and the absence of Philadelphia chromosome makes a diagnosis of CML unlikely. .* ***The patient in question has an elevated platelet count (> 600 x $10^9$/L) and only mild elevation of WBC count (12 x $10^9$/L both of which are consistent with a diagnosis of Essental thrombocythemia / thrombocytosis.***
***Essential Thrombocytosis is the single best option of exclusion.***

| Essential Thrombocytosis - CMDT / Robbins | Myeloprotiferative Disorders |
|---|---|
| • Diagnosis of exclusion<br>• ***Elevated Platelet count is the hall mark (usually >600 x $10^9$/L)***<br>• ***White cell count is only mildly elevated***<br>• Haematocrit is normal<br>• Philadelphia chromosome absent | Chronic Myeloid leukaemia<br>Polycythemia vera<br>Essential thrombocytosis<br>Myelofibrosis |

| | White cell count | Haematocrit | Platelet count | Red cell morphology | pH chromosome |
|---|---|---|---|---|---|
| CML | ↑↑ | N | N or ↑ | N | +ve |
| Myelofibrosis | N or ↓ or ↑ | N or ↓ | ↓ or N or ↑ | Abnormal | -nt |
| Polycythemia vera | N or ↑ | ↑ (↑Hb) | N or ↑ | N | -nt |
| Essential Thrombocytosis | N or ↑ | N | ↑↑ | N | -nt |

**Robbins 7th / 619 : Polycythemia :** ***The Haemoglobin concentration ranges from 14 to 28 gm/dL with Haematocrit values of 60% or more.***

***Presence of Markedly elevated Platelet count and mild elevation of white cell count in the absence of raised Haemoglobin levels suggests a diagnosis of essential thrombocytosis by exclusion.***

## Lymphomas & Chronic Leukemias

### Hodgkin's Lymphoma

**207. Answer is A (Lymphocyte predominant):** Harrison 18th/p 935 *Harrisons 17th/699; Robbins 7th/689*

*Lymphocyte predominant Hodgkin's disease is now recognized as an entity distinct from classical hodgkin's disease. Nodular Lymphocyte predominant hodgkins disease has a number of characteristic that suggest its relationship to Non-Hodgkins lymphoma.*

**Hodgkin's Disease**

| Classical Hodgkin's Disease | Histogenetically distinct subtype of Hodgkins Disease |
|---|---|
| Variants/Subtypes | Variant/Subtype |
| *Mixed cellularity*<br>*Nodular sclerosis*<br>*Lymphocyte Rich*<br>*Lymphocyte Depletion* | *Lymphocyte predominant*<br>*(Nodular Lymphocyte Predominant)* |
| Characterized by: | Characterized by |
| • *Frequent Reed sternberg cells*<br>• *Characteristic immunophenotype*<br>*CD 15 positive; CD 30 positive*<br>*CD 45 Negative* | • *Rare Reed Sternberg cells*<br>(Frequent Lymphocytic and Histocytic variants (Popcorn cells))<br>• Characteristically different immunophenotype<br>*CD 15 Negative : CD 30 Negative*<br>*CD 45 Positive* |

*Characteristic R.S cells are less frequent in nodular sclerosis variant of Hodgkins but these cells are characteristically positive for CD 15 and CD 30 and negative for CD 45*

**208. Answer is B (Read Sterberg cells):** *Robbins 7th/686*

*Hodgkin's Lymphoma is characterized morphologically by the presence of distinctive neoplastic giant cells called Read – Sternberg cells* -Robbins 7th/686

**209. Answer is D (Lymphocyte Predominant Hodgkin's disease):** *Robbins 7th/687,688,689)*

*Lympho-Histiocytic variants (L and H cells) have a delicate multilobed nucleus resembling a popcorn kernel and are also called popcorn cells.*

***Lymphohistiocytic variants are specific to lymphocyte predominance subtype of Hodgkin's Lymphoma.***

**Variants of Reed Sternberg cells**

| Lacunar variant | Mononuclear variant | Lymphohistiocytic variant (Popcorn cell; L and H cells) |
|---|---|---|
| R.S cells variant with a folded or multilobate nuclei and abundant pale cytoplasm which gives the appearance of a nucleus silting in an empty hole (lacunae) on histological sections | R.S cell variant with a single round or oblong nucleus | R.S cell variant with multiple folded or convoluted nuclear contour resembling a popcorn kernel (popcorn cell variant) |
| Characteristically seen in | Characteristically seen in | Characteristically seen in |
| *Nodular Sclerosis subtype* | *Mixed cellularity subtype*<br>*Lymphocyte Rich Subtype* | *Lymphocyte predominance variant* |

**210. Answer is A (Lacunar cells):** *Read text below*

*Lacunar cells are characteristic of nodular subtype of Hodgkins lymphoma.*

| Hodgkins lymphoma subtypes | Red Sternberg cells variant |
|---|---|
| Nodular sclerosis | Lacunar cells $^{Q}$ |
| Mixed cellularity | Mononuclear variant$^{Q}$ |
| Lymphocyte predominance | Popcorn cell $^{Q}$ (Lymphocytic variant) |
| Lymphocyte depleted | Reticular variant (more cellular) |

**211. Answer is A (Nodular sclerosis):** Harrison 18th/p 934 *Harrison 17th / 699; API 8 th / 903; Chandrasoma Taylor 3rd/ 457, 458*

*Nodular sclerosis is the most common subtype worldwide.*

The Hodgkin's lymphomas may be classified into four subtypes according to the Rye's classification.

| Hodgkins lymphoma subtypes in order of frequency |
|---|
| 1. Nodular sclerosis (30-60%) |
| 2. Mixed cellularity (20-40%) |
| 3. Lymphocyte predominance (< 10%) |
| 4. Lymphocyte depleted (< 10%) |

Incidence: NS > MC > LP > LD

*Note: WHO classification recognizes another subtype of Hodgkins called 'Lymphocyte Rich' subtype*

**212. Answer is C (Mixed cellularity):** *Chandrasoma Taylor 3rd/ 459; API 6th/ 928; API 8th/903*

*'While nodular sclerosis is the most common subtype in the developed countries, the mixed cellularity type is most common in developing countries.' - API 6th/928*

*As the questions specifically asks about the most common variant in India mixed cellularity is undoubtedly the single best answer.*

**213. Answer is A (Lymphocyte Predominance):** *Chandrasoma Taylor 3rd/ 459*

*Lymphocyte predominant type of Hodgkins lymphoma is associated with the best prognosis.*

| Variant | 5 years survival |
|---|---|
| *Lymphocyte predominance* | *90%* |
| *Nodular sclerosis* | *70%* |
| *Mixed cellularity* | *50%* |
| *Lymphocyte depletion* | *40%* |

Prognosis: LP > NS > MC > LD

**Remember one characteristic each, of each variety**

| | |
|---|---|
| • Lymphocytic predominant | *Best prognosis* $^{Q}$ |
| • Mixed cellularity | *M.C. type in India* $^{Q}$ |
| • Lymphocytic depleted | *Worst prognosis* $^{Q}$ |
| • Nodular sclerosis | *M.C. type (all over the world)* $^{Q}$ |

Note: *WHO classification recognizes another subtype of Hodgkins Lymphoma called 'Lymphocyte Rich' subtype.*

**214. Answer is A (Lymphocyte predominance):** *Chandrasoma Taylor 3rd/ 459*

*Lymphocyte predominant type of Hodgkins lymphoma is associated with the best prognosis.*

**215. Answer is A (CD15 and CD30):** *Robbins 7th/688, Harrisons / 16th /655*

*The tumor cells in Hodgkins Lymphoma are characteristically positive for CD15 and CD30 and negative for CD45.*
*– Robbins 7th/688*

*Lymphocyte predominance Hodgkins Lymphoma is the only histological subtype that does not express CD15 and CD30. This subtype expresses CD45 and is often considered as an entirely distinct category from classical Hodgkin's disease (Harrisons)*

| Hodgkins Lymphoma | Immunopheno type | Association with EBV | Read Sternberg Cell variant$^{Q}$ |
|---|---|---|---|
| Nodular Sclerosis | **CD15 +, CD30 +** | EBV – Ve$^{Q}$ | Lacunar cells$^{Q}$ (Occasional R-S-cells) |
| Mixed cellularity | **CD15 +, CD30 +** | EBV + Ve$^{Q}$ (70%) | Classic Reed Sternberg cells$^{Q}$ |
| Lymphocyte depletion | **CD15 +, CD30 +** | EBV +Ve$^{Q}$ | Reticular variant$^{Q}$ (Frequent R-S cells) |
| Lymphocyte Predominance | CD15 –ve, CD30-ve CD20 +ve, CD45+ve (H17$^{th}$) | EBV – Ve$^{Q}$ | Popcorn cell variant$^{Q}$ |

**216. Answer is C (Atypical cells):** *Robbin's 7$^{th}$/686, 687*

***Atypical cells may be seen in some variants of Hodgkin's disease but they are not required for the diagnosis of Hodgkin's disease.***

Diagnosis of Hodgkin's disease

**Histopathological (In all cases)**

*Identification of R-S cells and their variants in the appropriate reactive cellular background remains the diagnostic sine qua non* – 'Blood' 2$^{nd}$/841

Reed Sternberg cells/Variants
Reactive cellular background

*Although RS cells are requisite for the diagnosis they must present in an appropriate background of non-neoplastic inflammatory cells (lymphocytes, plasma cells, eosinophils)*

**Immunohistochemical markers** (In difficult cases)

Immunohistochemical markers on tissue sections of biopsy material for CD 15 & CD30 provides vital clues in establishing diagnosis in difficult cases.

The tumor cells have a characteristic immunophenotypes: Positive for CD15 and CD30 and negative for CD45

Except lymphocyte predominant variant which is CD15 & CD30 negative CD45 positive

**217. Answer is A (CNS is the commonest site of involvement) :** Harrison 18th/p 934 *Harrison 14$^{th}$/ 708, Harrison 15$^{th}$/ 725, Harrisons 16$^{th}$/ 654; Harrisons 17$^{th}$/ 699; API 8$^{th}$/ 903; Chandrasoma Taylor 3$^{rd}$/ 456, 457, 459*

*CNS involvement is an uncommon feature of Hodgkins disease*

**CNS involvement is an uncommon feature with Hodgkins disease:** This may occur as :

- Sudden spinal cord compression in advanced progressive disease.
- Headache and visual disturbance in very rare patients with intra-cranial Hodgkins disease.

**Reed stern berg cell is the characteristic cell in Hodgkins**, and the diagnosis of Hodgkins Lymphoma is still based entirely upon histological examination & the finding of classic Reed-Sternberg cell or one of its variants is considered essential for diagnosis.

***Plasms cells, Eosinophils and Neutrophils are seen in the reactive background***

Histology in Hodgkins shows distinctive Reed Sternberg cells (few) that are admixed with variable number of Lymphocytes, plasma cells, histocytes, eosinophills neutrophils and fibroblasts.

**Mediastinal involvement is particularly common with nodular sclerosis variant.**

**Certain Distincitive Features Seen In Nodular Sclerosis Variant**

- it is the most common variant. $^{Q}$
- it is the only variant more common in females. $^{Q}$
- mediastinal involvement is particularly common. $^{Q}$
- large Reed Sternberg cell variants - 'Lacunar cells' $^{Q}$ - are present on histology.
- it has a good prognosis $^{Q}$ {2nd best, following Lymphocyte predominance (best)}

**218. Answer is B (Cervical):** *William's Manual of Hematology 8th/ 440*

*The most common lymph nodes involved in Hodgkins Lymphoma are the cervical lymph nodes.*

**The most common lymph nodes involved in Hodgkin's Lymphoma are cervical lymph nodes and supraclavicular lymph nodes (60-70%)**

*'Detection of an unusual mass or swelling in the superficial, supra-diaphragmatic lymph nodes (60–70% cervical and supraclavicular, 15–20% axillary) is the most common presentation of Hodgkin's Lymphoma. Only 15 to 20 percent of patients have sub-diaphragmatic disease at presentation' – William's Manual of Hematology*

**219. Answer is C (Cerebellar degenerative disease):** *Harrison 18th/p 934; Harrison 16th/572-573; Harrison 17th/ 699*

*Hodgkin's Lymphoma is associated with prominent or pure paraneoplastic cerebellar degeneration.*

| Cancer | Syndrome | Antibody |
|---|---|---|
| Hodgkins Lymphoma | Paraneoplastic cerebellar degeneration (PCD) | Anti Tr. |

**Paraneoplastic Cerebellar degeneration**

**Pure crebellar degeneration**
- Breast and Gynaecological cancers (Anti Yo Antibodies)
- Hodgkins Lymphoma (Anti Tr Antibodies)

**Subacute Cerebellar degeneration**
- Small cell carcinoma lung
- Thymoma
- Neuroblastoma

**220. Answer is C (Absolute lymphocyte count < 600/mm3):** *'Blood' by Handen, Lux and Stossel (2002)/852,854; Hoffman 4th/1351,1352; William's 7th/1473*

*An absolute Lymphocyte count of <600 is a poor prognostic factor in Hodgkin's lymphoma.*

**Prognostic factors in Hodgkins lymphoma**

**Poor prognostic factors for advanced disease**
- Male Gender
- Age>45 years
- Stage IV Disease
- Serum Haemoglobin < 10g
- Serum Albumin < 4 g
- WBC count > 15,000/$mm^3$
- Absolute lymphocyte count < 600$mm^3$

*These factor predict relapse of advanced disease*

**Poor prognostic factors in Localized disease**
- Male Gender
- Age >50 years
- Histological subtype (mixed cellularity and lymphocyte Depletion)
- Elevated ESR
- Mediastinal mass >1/3 of thoracic diameter (Mediastinal/thorax ratio > 35%)
- Number of involved sites with the same side of diaphragm > 4
- Presence of systemic symptoms ('B' symptoms)

*These factors predict prognosis in patients with clinical stages I and II in Hodgkin's disease.*

**221. Answer is A (Younger age):** *Refer previous questions*

*Young age < 45 years is a good prognostic feature. Old age (> 50 years) is a poor prognostic factor*

***Lymphocyte depletion subtype, presence of mediastinal disease and systemic manifestation** are all established poor prognostic factors*

***Stomach involvement** reflects advanced stage of disease and is likely to be associated with a poor prognosis.*

**222. Answer is B (stage IIB):** *Harrison 18th/p 924 Harrisons 17th/691*

*The patient is presenting with involvement of two lymph node regions on the same side of diaphragm (stageII) along with presence of systemic symptoms (Group B). This patient can thus be staged as having stage II B disease.*

**THE ANN ARBOR STAGING SYSTEM FOR HODGKIN'S DISEASE**

| Stage | Definition |
|---|---|
| I | Involvement of a single lymph node region or lymphoid structure (e.g., spleen, thymus, Waldeyer's ring) |
| II | Involvement of two or more lymph node regions on the same side of the diaphragm (the mediastinum is a single site; hilar lymph nodes should be considered "lateralized" and, when involved on both sides, constitute stage II disease) |
| III | Involvement of lymph node regions or lymphoid structures on both sides of the diaphragm |
| III-1 | Subdiaphragmatic involvement limited to spleen, splenic hilar nodes, celiac nodes, or portal nodes |
| III-2 | Subdiaphragmatic involvement includes paraaortic, iliac, or mesenteric nodes plus structures in III-1 |
| IV | Involvement of extranodal site(s) beyond that designated as"E" more than one extranodal deposit at any location Any involvement of liver or bone marrow. |
| A | No symptoms |
| B | Unexplained weight loss of >10% of the body weight during the 6 months before staging investigation<br>Unexplained persistent, or recurrent fever with temperatures >38°C during the previous month<br>Recurrent drenching night sweats during the previous month |
| E | Localized, solitary involvement of extralymphatic tissue, excluding liver and bone marrow. |

**223. Answer is C (Radiotherapy only):** *Harrison 18th/p 935 Harrisons 17th/700; William's Hematology 7th/1470*

*Regional Radiotherapy is the treatment of choice for localized/limited stage disease nodular lymphocyte predominant hodgkin's Lymphoma*

*'Nodular lymphocyte predominant Hodgkins lymphoma NLPHL presents as asymptomatic limited stage disease in most patients. Most patients present with peripheral lymph nodes in neck, axilla or groin and are classified as limited stage IA disease. Because of the low likelihood of occult disease and tendency of disease to remain localized for years, regional RT is considered treatment of choice'.-Williams 7th/1471*

***The patient in question presents with a single cervical lymph node and hence can be classified as having stage 1A disease with nodular lymphocyte predominant Hodgkin's lymphoma. Regional RT is the treatment of choice for such patients.***

**Treatment of Hodgkin's Lymphoma**

**Classical Hodgkin's Lymphoma**

| Limited Stage Disease | Advanced Disease |
|---|---|
| (Favourable/unfavourable) (Stage I, II) | Stage III, IV |
| Combined Modality treatment with Radiotherapy and chemotherapy is the treatment of choice<br>Limited Stage Disease (I, II) is primarily managed by a combination of chemotherapy (CT) and Radiotherapy (RT) (CT→RT) | Chemotherapy is the treatment of choice<br>Advanced stage disease is primarily managed by chemotherapy<br>Radiotherapy may be used in advanced disease for bulky disease or residual disease after chemotherapy (PTO) |
| CT + RT | CT ( ± RT ) |

**Nodular Lymhocyte predominant Hodgkin's Lymphoma**

| Limited Stage Disease | Advanced Disease |
|---|---|
| Stage I, II | Stage III, IV |
| Radiotherapy alone is the treatment of choice (Involved Field RT or Regional RT may be used)<br>*Some clinicians favour no treatment and merely close follow up* | Chemotherapy is the treatment of choice<br>Advanced stage disease is primarily managed chemotherapy<br>*RT may be used in advanced disease for palliation only and in selected cases after chemotherapy.* |
| RT | CT (± RT) |

**224. Answer is A (Chemotherapy with Radiotherapy):** Harrison 18th/p 934 *Harrisons 17th/699: Williams 7th/1469-1471*

*Combined modality treatment with Chemotherapy and Radiotherapy is the treatment of choice in limited stage (stage I,II) Hodgkin's lymphoma with a classical Histological subtype.*

**Patient has limited Stage I Hodgkin's Lymphoma**

Patient in question presents with involvement of single lymph node region and hence can be staged as having stage I (Limited) disease.

| | |
|---|---|
| Stage I | Disease Involvement of single lymph node region. |

***Patient has a classical Hodgkin's Lymphoma of nodular sclerosis subtype***

The presence of frequent Lacuner cells suggests a diagnosis of nodular sclerosis

**Hodgkins lymphoma**

| Classical Hodgkin's | Non classical Hodgkins |
|---|---|
| Nodular sclerosis (Lacunar cells)<br>Mixed cellularity (Mononuclear cells)<br>Lymphocyte rich (Mononuclear cells)<br>Lymphocyte depletion | Nodular lymphocyte predominance Hodgkins<br>NLPHL (popcorn cell/lymphohistiocytic cell) |

**The treatment of choice for limited Stage I Classical Hodgkins Lymphoma is combined modality therapy with Chemotherapy and Radiotherapy**

**225. Answer is B (Radiatiotherapy is best):** Harrison 18th/p 934 *Harrison 17th/; CMDT 2008/453; 2009/459*

*Patients with localized stage IA disease are best treated with Radiation therapy to involved fileds.*

*Initial treatment with a brief course chemotherapy before radiuotherapy may improve the outcome, however, amongst the options provided the treatment of choice remains radiotherapy.*

Treatment of Hodgkins Disease

| Stage I (A) and Stage II (A) | Stage III and Stage IV and patient with group B symptoms |
|---|---|
| ***Corner stone of treatment is Radiotherapy to involved field***<br>*Initial treatment with a brief course of chemotherapy improves outcome*<br>*Treatment of choice is a brief course of chemotherapy followed by Radiotherapy to sites of node involvement* | ***Cornerstone of treatment is combination chemotherapy***<br>*Radiotherapy may be administered after chemotherapy in those who obtain only a poor partial response, but it has not shown to improve outcome in patients who achieve complete remission after combination chemotherapy.* |

**226. Answer is C (ABVD):** Harrison 18th/p 934 *Harrison 17th/Manual of Oncology 6th/443*

*ABVD is the chemotherapy regimen of choice in Hodgkins lymphoma*

*'Chemotherapy with ABVD is considered the standard first line treatment for most patients and is superior to MOPP in efficacy and toxicity profile'- Manual of Clinical Oncology 6th/443*

| Regimen | Agents | Comments |
|---|---|---|
| ABVD | Doxorubicin<br>Bleomycin<br>Vinblastine<br>Dacarbazine | • *First line treatment of choice*<br>• *Most popular regimen in United States*<br>• *More effective than MOPP*<br>• *Lesser incidence of Sterility and secondary malignancies than MOPP*<br>• *More satisfactory than MOPP and ABVD in alternating cycles or MOPP/ABV Hybrid* |
| MOPP | Mechlorethamine<br>Vincristine<br>Procarbozine<br>Prednisolone | • *Less effective and more toxic than ABVD*<br>• *Higher incidence of sterility and secondary malignancies than ABVD* |

| | | |
|---|---|---|
| Stanford V | • Doxorubicin<br>• Bleomycin<br>• Vinblastine<br>• Mechlorethamine<br>• Vincristine<br>• Prednisolone<br>• Etoposide<br>+<br>Radiotherapy | • *Excellent results but still under investigations/ Trial* |
| BEACOPP | | • *Popular in Europe*<br>• *Not fully evaluated* |

**227. Answer is B (Sterility is more frequent complication of ABVD than MOPP):** Harrison 18th/p 935 *Harrison 17th/699; Harrison 's Manual of Oncology (2007)/218*

***Sterility is more frequent complication of MOPP than ABVD.***

Infertility and Treatment of Hodgkins Lymphoma

- Infertility is a concern for all patients undergoing treatment
- Risk of infertility is age related – Risk is increased in old age (younger patients are more likely to recover fertility)
- ***Risk of infertility is more with MOPP than ABVD***
  (*Treatment with ABVD rather than MOPP increases the chances to retain fertility* - Harrison)

## Non Hodgkins Lymphoma and Leukemia

**228. Answer is B (REAL Classification) :** *Robbins 7th/668; AJC Cancer staging Handbook API 8 th/905*

***In 1994, a group of hematopathologists, oncologists and molecular biologists came together (International Lymphoma Study Group) and introduced a new classification, called the 'Revised European-American Classification of Lymphoid Neoplasms (REAL).***

*WHO has now reviewed and updated the real classification resulting in inclusion of additional rare entities.*

**WHO Classification / Modified 'REAL' Classification**

**I. Precursor B-cell Neoplasm**
- Precursor-B lymphoblastic leukemia/lymphoma

**II. Peripheral B-Cell Neoplasms**
- Chronic lymphocytic leukemia/small lymphocytic lymphoma
- B-cell prolymphocytic leukemia
- Lymphoplasmacytic lymphoma
- Splenic and nodal marginal zone lymphomas
- Extranodal marginal zone lymphomas
- Mantle cell lymphoma
- Follicular lymphoma
- Marginal zone lymphoma
- Hairy cell leukemia
- Plasmacytoma/plasma cell myeloma
- Diffuse large B-cell lymphoma
- Burkitt lymphoma

**III. Precursor T-Cell Neoplasms**
- Precursor-T lymphoblastic leukemia/lymphoma

**IV. Peripheral T-Cell and NK-Cell Neoplasms**
- T-cell prolymphocytic leukemia
- Large granular lymphocytic leukemia
- Mycosis fungoides/Sezary syndrome
- Peripheral large cell lymphoma, unspecified
- Anaplastic large cell lymphoma
- Enteropathy-associated T-cell lymphoma
- Hepatosplenic γδ T-cell lymphoma
- Adult T-cell leukemia/lymphoma
- NK/T-cell lymphoma, nasal type
- NK cell leukemia

**V. Hodgkins Lymphoma**
- Classical subtypes
  - Nodular sclerosis
  - Mixed cellularity
  - Lymphocyte-rich
  - Lymphocyte depletion
- Lymphocyte predominance

**229. Answer is B (Angiocentric Lymphoma) :** Harrison 18th/p 920 *Robbins 7th / 671; Harrison 16th / 654; Harrison 17th / 688*

***Angiocentric Lymphoma is a type of T cell lymphoma that has been linked to the Epstein Barr Virus.***

Angiocentric Lymphoma has been classified as a Peripheral T cell Lymphoma : - *Harrison 16th*
'Extranodal T/NK cell lymphoma of nasal type has also been called angiocentric lymphoma' - Harrison
(Also called Lethal Midline granuloma)

| Classification of Non Hodgkin Lymphoma | |
|---|---|
| **B cell Neoplasms** | **T cell Neoplasms** |
| Neoplasms of immature B cells | Neoplasms of immature T cells |
| Precursor B cell Acute Lymphoblastic leukaemia / lymphoma | Precursor T-cell Acute Lymphoblastic leukaemia / Lymphoma |
| Neoplasms of mature B cells | Neoplasms of mature T cells / NK cells |
| • ***Burkitt's lymphoma***[Q]<br>• ***Hairy cell leukemia***[Q]<br>• ***Mantle cell lymphoma***[Q]<br>• Solitary plasmacytoma / Multiple Myeloma[Q]<br>• Small lymphocytic lymphoma / Chronic lymphocytic leukaemia (CLL)<br>• Follicular lymphoma<br>• Diffuse large B cell lymphoma<br>• Extranodal marginal zone lymphoma (MALT Type) | • Mycosis fungoides : Cutaneous T cell lymphoma<br>• Adult T cell lymphoma / Leukemia<br>• Anaplastic Large T cell / Null cell Lymphoma<br>• Peripheral T cell Lymphoma<br>○ Angioimmunoblastic Lymphoma<br>○ ***Angiocentric Lymphoma*** (Extra-nodal T/NK cell Lymphoma<br>○ Enteropathy type intestinal lymphoma<br>○ Hepatosplenic lymphoma<br>○ Subcutaneous Panniculitis - like lymphoma<br>• T cell granular lymphocytic lymphoma |

**230. Answer is B (IgM):** Harrison 18th/p 942, 943 *Harrison's 17th/-706 ' Surgicla pathology of Head & Neck' by Barnes 2nd/ 1270, 1271*

***Plasmacytoid Lymphomas may be associated with a monoclonal IgM paraprotein (Waldenstrom's Macroglobulinemia).***

Plasmacytoid Lymphocyte Type Malignant Lymphoma / Plasmacytoid Lymphoma

- This is a ***B cell neoplasm***[Q] that is associated with plasmacytoid differentiation of lymphocytes
- Plasmacytoid lymphocytes are transitional forms between lymphocytes and plasma cells
- ***These may be associated with a monoclonal IgM paraprotein and are thus considered the histological counterparts of Waldenstrom's Macroglobulinemia***
- Synonyms include immunocytoma

  Kiel Classification : Malignant Lymphoma, Lymphoplasmacytoid immunocytoma
  REAL Classification: Lymphoplasmacytoid Lymphoma / Immunocytoma
- These are ***low grade lymphoid neoplams***[Q] that occur in middle aged or older individuals.

**231. Answer is D (Hemoglobin and Albumin)** Harrison 18th/p 925 *'Harrison 17th Ed / 692*

***'International prognostic index' does not include Hemoglobin and Albumin as prognostic factors.***

| Prognostic Factors according to International Prognostic Index for NHL | |
|---|---|
| 1. *Age*[Q] | : *(Age ≤ 60 years carries adverse prognosis)* |
| 2. *Stage*[Q] | : *(Ann Arbor stage III or IV carries adverse prognosis)* |
| 3. *LDH levels*[Q] | : *(Elevated LDH levels above normal carry adverse prognosis)* |
| 4. *Performance status*[Q] | : *(P.S ≥ 2 (ECOG) or ≤ 70 (Karnofsky) carries adverse prognosis)* |
| 5. *Number of Extranodal sites involved*[Q] | : *(>1 extranodal site* involvement carries adverse prognosis) |

**International Prognostic Index for NHL**

*Five clinical risk factors:*
- *Age ≥ 60 years*
- *Serum lactate dehydrogenase levels elevated*
- *Performance status ≥ 2 (ECOG) or ≤ 70 (Karnofsky)*
- *Ann Arbor stage III or IV*
- *> 1 site of extranodal involvement*

**232. Answer is B (Diffuse, small cleaved cell):** *Robbins 5th/638, Robbins 7th/does not mention the working formulation*

***Working formulation of NHL*** for clinical usage is as follows:

| **Low grade** |
|---|
| 1. Small lymphocytic ♀ |
| 2. Follicular, predominantly small cleaved cell ♀ |
| 3. Follicular, mixed, small cleaved and large cell. ♀ |
| **Intermediate grade** |
| 1. Follicular predominantly large cell ♀ |
| 2. Diffuse small cleaved cell |
| 3. Diffuse mixed small and large cell. |
| 4. Diffuse large cell. |
| **High grade** |
| 1. Large cell immunoblastic ♀ |
| 2. Lymphoblastic ♀ |
| 3. Small non cleaved cell. ♀ |

*Note that all varieties of diffuse fall in the intermediate grade category only.*

**233. Answer is C (Mycosis fungoides):** *Repeat Harrison 15th/ 724; Robbins 5th/ 638; (Harrison 16th/ Robbins 7th/ does not mention the working formulation)*

*Mycosis fungoides is included in the Miscellaneous group. ♀ It does not fall in the intermediate grade.*
*All' diffuse' fall into intermediate grade.* Intermediate grade includes only one more variant, which is follicular, large cell.

**Intermediate grade includes:**

| |
|---|
| 1. Diffuse small cleaved ♀ |
| 2. Diffuse mixed small and large cell ♀ |
| 3. Diffuse large cell, and ♀ |
| 4. Follicular large cell ♀ |

**234. Answer is A (Diffuse large cell):** *Repea Harrison 15th/ 724; Robbins 5th/ 638t*

*Diffuse large cell lymphoma is the most malignant, amongst the options provided.*
*Although Follicular large cell and Diffuse varieties are both classified in the intermediate grade of the 'working formulation of NHL', in general,* ***'lymphomas with a follicular histological pattern are of a lower grade (longer survival times) than those with a diffuse pattern'*** *– (Chandrasoma Taylor 2nd/ 439)*

**235. Answer is A (Diffuse large B-cell lymphoma):** *Ann Oncol. 2000;11 Suppl 1:63-7.'Distribution of various subtypes of non-Hodgkin's lymphoma in India: a study of 2773 lymphomas using R.E.A.L. and WHO Classifications' (http://www.ncbi.nlm.nih.gov/pubmed/10707782)*

***The most common variant of Non-Hodgkin's Lymphoma in India is Diffuse Large B cell Lymphoma***
*Diffuse Large B cell Lymphoma is also the most common variant of Non-Hodgkin's Lymphoma in the United States (Western Data)*

> *'The majority of Non-Hodgkin's Lymphoma (NHL) in India are B-cell Lymphomas (around 80 percent). The distribution of Non-Hodgkin's Lymphoma (NHL) subtypes in India shows important differences with those from the rest of the world. Diffuse large B-cell lymphoma remains the most common form of NHL as in Western Data. However, Follicular lymphoma and mantle-cell lymphoma are less common in India compared to Europe and the USA. T cell Lymphomas account for approximately 16 percent of all NHL. T-cell lymphoblastic lymphoma and anaplastic large T/null cell lymphoma are more prevalent in India. Peripheral T-cell lymphomas and T/NK-cell lymphomas of nasal and nasal types, which are common in many other Asian countries, are less prevalent.'*

*Taken from : 'Distribution of various subtypes of non-Hodgkin's lymphoma in India: a study of 2773 lymphomas using R.E.A.L. and WHO Classifications' (http://www.ncbi.nlm.nih.gov/pubmed/10707782)*

**236. Answer is A (Immunoblastic Lymphoma):** *Harrison's 18th/ 1566*

***The most common lymphomas seen in HIV Patients are Immunoblastic Lymphomas. Majority of these are Diffuse Large B Cell Lymphomas (DLBLS).***

| **Three Main categories of Lymphomas seen in HIV Patients** |
|---|
| • Immunoblastic Lymphomas (~60%) (Majority of these are Diffuse Large B cell Lymphomas) |
| • Small Non- cleaved cell lymphomas or Burkitt's lymphoma (~20%) |
| • Primary CNS Lymphoma (~20%) |

**237. Answer is A (Primary Effusion Lymphoma):** *Harrison's 18th/ 1566*

***Primary Effusion Lymphoma (PEL) is a rare variant of Immunoblastic Lymphomas seen primarily in HIV infected patients.***

**Primary Effusion Lymphoma (PEL) is a rare variant of Immunoblastic Lymphomas seen primarily in HIV infected patients**

*'Two variants of Immunoblastic Lymphomas seen primarily in HIV infected patients are Primary Effusion Lymphoma(PEL) and its solid variant Plasmacytic lymphoma of the oral cavity' Harrison 18th/ 1566*

**Centroblastic Lymphoma and Anaplastic Lymphomas are variants of Diffuse Large B call Lymphomas and are distinct entities from Immunoblastic Lymphomas**

| Morphologic Variants of Diffuse Large B Cell Lymphomas ( DLBCL) |
|---|
| • Centroblastic |
| • Immunoblastic |
| • Anaplastic |

## Burkitt's Lymphoma

**238. Answer is B (8 – 14 translocation):** Harrison 18th/p 931 *Harrison 17th / 696; Chandrasoma Taylor 3rd/ 296*

***Presence of t (8; 14) or one of its variants t (2; 8) or t (8; 22) can be confirmatory – Harrison 16th/ 652.***

**Important translocation to be remembered**

| Translocation | Associated Malignancy |
|---|---|
| t 8 – 14 | Burkitt's lymphoma ♀ |
| | ALL (FAB type L3) |
| | Immunoblastic B cell lymphoma ♀ |
| t 15-17 | Promyelocytic Leukemia ♀ ($M_3$- AML) |
| t 4 – 11 | ALL ♀ |
| t 11 – 14 | CLL ♀, *Mantle cell lymphoma* |
| t 14 – 18 | B cell lymphomas ♀ |

**239. Answer is D (Burkitt's Lymphoma):** Harrison 18th/p 931, 923 *Harrison's 17th/696, 690; Wintrobe's Hematology 12th/2082, 1604; Atlas of Hematologic Neoplasms by Tsieh Sun/26; Cancer Cytogenetics by Heim, Mitelman 3rd/326; Clinical Malignant Hematology by Sekeres, Kalaycio, Bolwell 1st (2007)/114*

***Translocation t(2:8)(p12:q24) is associated with Burkitt's lymphoma / leukemia.***

*'The hallmark of Burkitt lymphoma is the t(8;14)(q24;q32) and its variants, t(2;8)(p12; q24) and t(8;22)(q24;q11) '.*
*-Cancer Cytogenetics by Heim, Mitelman 3rd/326; Clinical Malignant Hematology by Sekeres, Kalaycio, Bolwell 1st (2007)/114*

*'Demonstration of very high proliferative fraction and the presence of the t(8;14) or one of its* ***variants t(2;8)*** *or t(8:22) can be confirmatory of Burkitt's lymphoma / leukemia' - Harrison's 17th/696*

| Neoplasm | Translocation | Genes involved |
|---|---|---|
| Burkitt | *t(8;14)(q24:q32) most common♀* | *c-MYC: IgH (heavy chain)* |
| | *t(2;8)(p12;q24)* | *Igκ: c-MYC (light chain)* |
| | *t(8;22)(q24:q11)* | *c-MYC : Igλ (light chain)* |

**240. Answer is A (t(8:14)):** Harrison 18th/p 931, 923 *Harrison's 17th/696, 690*

***t (8; 14) is the most common translocation seen in association with Burkitt's Lymphoma***

*'Demonstration of very high proliferative fraction and the presence of the* ***t (8; 14)*** *or one of its variants t (2; 8) or t(8:22) can be confirmatory of Burkitt's lymphoma / leukemia' - Harrison's 17th/696*

**Translocations in Burkitt's Lymphoma**

Burkitt's lymphoma / leukemias are associated with reciprocal translocations involving the ***c-myc gene on chromosome 8***

| Most common Translocation (70% cases) | Less common translocations |
|---|---|
| ***t (8; 14):*** c- myc gene on chromosome 8 and IgH heavy chain on chromosome 14 | **t (8; 22)** c- myc gene on chromosome 8 and λ-light chain on chromosome 22<br>**t (2; 8) :** c- myc gene on chromosome 8 and κ-light chain on chromosome -2 |

**241. Answer is A (EBV):** *Harrison 17th /689; Harrison's 18th/921*

***Burkitt's Lymphoma is typically associated with Epstein Barr virus (EBV).***

*EBV is associated with upto 95% of cases of Endemic Burkitt's Lymphoma.*
*EBV is associated with approximately 30% of cases of Sporadic Burkitt's Lymphoma and Immune Deficiency associated Burkitt's Lymphoma.*

**Infectious Agents Associated with the Development of Lymphoid Malignancies**

| Infectious Agent | Lymphoid Malignancy |
|---|---|
| Epstein-Barr virus | • *Burkitt's lymphoma*<br>• *Post–organ transplant lymphoma*<br>• *Primary CNS diffuse large B cell lymphoma*<br>• *Hodgkin's disease*<br>• *Extranodal NK/T cell lymphoma, nasal type* |
| HTLV-I | • *Adult T cell leukemia/lymphoma* |
| HIV | • *Diffuse large B cell lymphoma*<br>• *Burkitt's lymphoma* |
| Hepatitis C virus | • *Lymphoplasmacytic lymphoma* |
| *Helicobacter pylori* | • *Gastric MALT lymphoma* |
| Human herpesvirus 8 | • *Primary effusion lymphoma*<br>• *Multicentric Castleman's disease* |

CNS, central nervous system; HIV, human immunodeficiency virus; HTLV, human T cell lymphotropic virus; MALT, mucosa-associated lymphoid tissue; NK, natural killer.

**242. Answer is D (Radiotherapy is the treatment of choice):** Harrison 18th/p 931 *Harrison 17th/; Robbins 7th/678*

***The treatment of choice for Burkitt's Lymphoma is chemotherapy and not Radiotherapy.***

*'Burkitt's lymphoma responds well to short term high dose chemotherapy. Treatment of Burkitt's lymphoma in both children and adults should begin within 48 hours of diagnosis and involves the use of intensive combination chemotherapy regimens' – Harrisons*

**Burkitt's Lymphoma is a B cell lymphoma**

*Burkitt's Lymphoma are tumors of mature B cells* – Robbins 7th/677

**t (8;14) translocation is the most common translocation in Burkitt's Lymphoma**

Burkitt's lymphomas are associated with translocation of the c-MYC gene on chromosome 8.

Translocation
t (8; 14)
t (8; 22)
t (2; 8)

**Burkitt's Lymphoma may present with an abdominal mass**

- Most Burkitt's Lymphoma presents at extranodal sites but may present with lymphadenopathy
  Extranodal sites of involvement include the mandible and abdominal viscera
  *'Burkitt's Lymphomas may present with peripheral lymphadenopathy or an intraabdominal mass'* – Harrison
- CNS involvement is frequent
  The disease is rapidly progressive and has a propensity to metastasize to CNS, prophylactic therapy to CNS is therefore mandatory.
- *Burkitt's Lymphoma is the most rapidly progressive human tumor* – Harrison

## Hairy Cell Leukemia

**243. Answer is B (Results from an expansion of Neoplastic T lymphocytes):** *Repeat: Harrison's 15th/725;Robbins 6th/668*

***Hairy cell leukemia isa 'B' cell neoplasm and is characterized by expansion of neoplasticB cells (not T lymphocytes)***

Hairy cell leukemia:

Hairy cell leukemia is a rare but distinctive form of chronic B cell leukemia that derives its name from the appearance of fine 'hair like projections'[Q] on the leukaemic cells (large B cells)

| | |
|---|---|
| • **Characteristic cytochemical feature:** | Presence of tartrate resistant acid phosphatase 'TRAP' [Q] in neoplastic B cells |
| • **Cellular features/ Markers**[Q] | • Hairy cells express the pan B cell markers CD 19 and CD 20 and monocyte associated antigen CD 11<br>• Plasma cell associated antigen (PCA-1) is also present – Robbins<br>• Expression of **CD 25**, IL2 and specific adhesion molecules – Harrison 14th/695 |
| • **Clinical features**<br>result largely from infiltration of bone marrow liver and spleen | • Present predominantly in the older age group > 40 years[Q]<br>• Massive splenomegaly[Q] (hepatomegaly is less common)<br>• Lymphadenopathy<br>• Pancytopenia[Q]<br>• Recurrent infections |
| • **Treatment** [Q] | • Current treatment of choice is with purine analogues – Cladribine[Q]<br>• Other drugs used<br>- Pentostotin[Q]<br>- Interferon α[Q]<br>• Splenectomy used to be the standard treatment earlier |

**244. Answer is B (B Cells):** Harrison 18th/p 920 *Harrison 16th/ 652; Harrison 17th/ 688; Robbins 6th/ 668, Robbins 7th/ 683*

***Hairy Cell Leukemia is a rare but distinctive B-cell neoplasm.***

**Hairy cell leukemia review :**

| |
|---|
| ***Presentation* is with a triad of :** |
| 1. Splenomegaly [Q] : often massive. However hepatomegaly is less common while lymphadenopathy is rare. |
| 2. Pancytopenia [Q] and thereby, resulting infections. |
| 3. Vasculitis like syndrome [Q] : Erythema nodosum and cutaneous nodules due to perivasculitis and PAN. |
| ***Course*** : Hairy cell leukemia follows an indolent course. [Q] |

**245. Answer is D (Hairy cell leukemia) :** Harrison 18th/p 920 *Harrison 17th/ 697;CMDT 2008/450; 2009/456; Robbins 7th/683*

***Presence of massive splenomegaly, and granulocytopenia, alongwith characteristic immunophenotypic features (specially CD103) suggests the diagnosis of Hairy cell leukemia. CD103 is exclusively positive in Hairy cell leukemia and thus leaves no doubt as regards the correct diagnosis.***

**Immunophenotypic features of Hairy cell leukemia.**

| CD markers | Surface immunoglobulins |
|---|---|
| Pan B cell markers : CD 19, CD 20 | Heavy chain : IgG |
| Monocytic associated antigen : CD11c, CD25, CD103 | Light chain : γ or λ |

| | SIg | CD5 | CD10 | CD11c | CD19 | CD20 | CD22 | CD23 | CD25 | CD103 |
|---|---|---|---|---|---|---|---|---|---|---|
| ***Hairy cell leukemia*** | -/+ | -/+ | - | ++ | + | + | ++ | -/+ | + | ++ |
| Mantle cell lymphoma | + | ++ | - | - | + | + | + | -/+ | - | - |
| CLL | +/- | ++ | - | -/+ | + | +/- | -/+ | ++ | -/+ | - |
| Prolymphocytic leukemia | ++ | + | - | -/+ | + | +/- | + | +/- | - | - |
| Splenic marginal lymphoma | + | -/+ | -/+ | + | + | + | +/- | -/+ | - | - |
| Lympho- plasmacytoma | +/- | -/+ | - | - | + | -/- | +/- | -/+ | +/- | - |

**246. Answer is A (Steroid):** Harrison 18th/p 931, 932 *Harrison 16th/ 652; Harrison 17th/ 697; Robbins 7th/ 683*

***Steroid has no role in treatment of hairy cell leukemia.***
Cladribine is the drug of choice. Clinical complete remissions with cladribine occur in majority of patients and long-term disease free survival is frequent.

**Treatment of hairy cell leukemia is chemotherapy with**

- Cladribine : Drug of choice.
- *Alpha-interferon* Q
- *Pentostatin* Q

***Splenectomy*** *used to be the standard treatment* of cytopenias resulting from Hairy cell leukemia

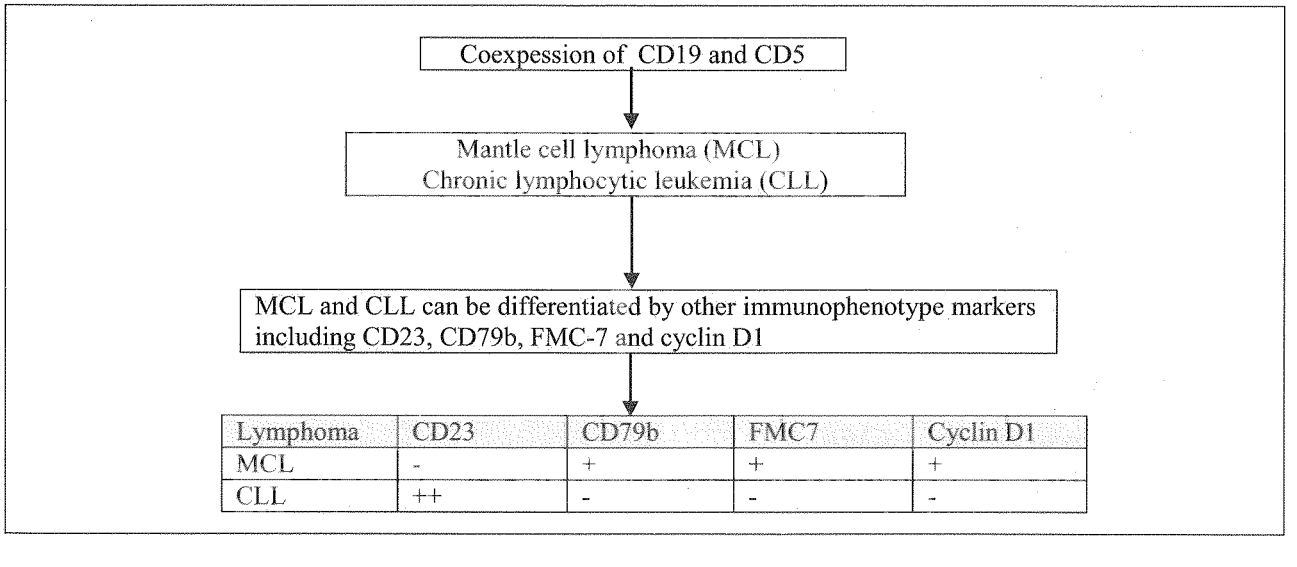
**247. Answer is B (Cladribine):** Harrison 18th/p 931, *Harrison 15th/ 724, Harrison 16th/ 652; Harrison 17th/ 697; CMDT 2005/ 494; 2009/456*

*"The treatment of choice is Cladribine Q (2 chlorodoxy adenosine) 0.14 mg /kg daily for 7 days" – CMDT*
*This is a relatively non-toxic drug that produces benefit in 95% of cases, and complete remission in more than 80%*

## Mantle Cell Lymphoma

**248. Answer is B (Mantle cell Lymphoma):** *Handbook of Human Immunology 2nd/245; Williams 7th/1347; Hoffman's 4th/1381*

***Coexpression of the B lymphocyte lineage marker CD 19 and T lymphocyte marker CD5 is unique to CLL and mantle cell Lymphoma. CLL can be differentiated from MCL be expression of CD79b and FMC-7 both of which are absent in CLL and positive in MCL- Handbook of clinical immunology 2nd/245***




| Lymphoma | CD23 | CD79b | FMC7 | Cyclin D1 |
|---|---|---|---|---|
| MCL | - | + | + | + |
| CLL | ++ | - | - | - |

*'CLL can be differentiated from MCL by expression of CD79b and FMC-7 both of which are absent in CLL/SLL and bright in MCL'* -Handbook of human Immunology 2nd/245

*'In contrast to CLL B cells mantle cell Lymphoma cells do not express CD23' – Williams 7th/1351*

**249. Answer is A (Mantle cell lymphoma):** Harrison 18th/p 928, 929 *Ackerman surgical pathology 8th/ 1721; Neoplastic histopathology 2nd/ 789; Robbins 7th/ 683; Harrisons 16th/ 648, 650; Harrison 17th/ 693, 694, 695*

***The given clinical profile is suggestive of mantle cell lymphoma as explained below.***

***Mantle cell lymphoma***

*Presents in the middle aged and the elderly* (Mean Age = 63 yrs – *Harrison 16th/ 648*).

| Clinical profile |
|---|
| - Painless lymphadenopathy<br>- Splenomegaly<br>- Occasional GI involvement |

**Immunocytochemical profile of Mantle Cell Lymphoma**

| CD markers | SURFACE immunoglobulins | Translocation |
|---|---|---|
| • Cells are positive for PAN B markers D 19, CD 2, CD 22, CD 24<br>• Cells are positive for CD 5<br>• Cells are negative for CD 23<br>• Cells are negative for CD 10 | • Moderately high levels of surface immunoglobulins heavy chains IgM & IgD<br>• B cells present bright K positivity (either K or λ light chain may be present) | t (11; 14) translocation 14 t (11; 14) translocation leads to increased expression of cyclin D1 |

## Chronic Lymphocytic Leukemia (CLL)

**250. Ans. Answer is D (All of the above):** *Harrison 18th /926; Wintrobe's Atlas of Clinical Hematology (2007)/138; Essentials in Hematology and clinical pathology' by Naik, Ras, Gupta (JP) 2012/202, 205, 204*

***CLL is commonly seen in individuals > 50 years (median age is about 65 year) and are typically chrachterized by the presence of increased number of mature small lymphocytes in the peripheral smear. Hepatosplenomegaly and lymphadenopathy may be seen.***

*'The physical examination may be unremarkable but common findings are hepatosplenomegaly and enlarged non tender, firm mobile lymph nodes in the cervical axillary and inguinal areas' - Wintrobe's Atlas of clinical Hematology*

| Diagnostic criteria of CLL are (Wintrobe's Atlas of Clinical Hematology) |
|---|
| 1. An absolute Lymphocytosis > 5x $10^9$/L<br>2. > 30% Lymphocytosis in a normocellular or hypercellular bone marrow<br>3. Monoclonal B cells with low levels of surface immunoglobulins and CD5 positivity |

**251. Answer is C (CLL) :** *Harrison 16th / 648; CMDT 2006 / 510; 2009/454-455*

***Incidental finding of Lymphocytosis (80,000/mcL) in an elderly and asymptomatic patient suggests the diagnosis of CLL.***

***Why is CLL the single best answer of choice here ?***

- *'CLL is a disease of older patients wth 90% of cases occurring after the age of 50 years and median age of presentation is 65 years'. – CMDT*

  ***The patient in question is aged 80 years and hence falls in the bracket of CLL.***
- *'Typical B cell CLL is often found incidentally when a complete blood count is done for another reason'. – Harrison 16th / 648*

***The patient in question is asymptomatic and the findings represent incidental observation on a full blood count done for an obscure reason.***

- *'The hallmark of CLL is absolute lymphocytosis. White cell count is usually greater than 20,000/mcL may be markedly elevated to several 100,000/mcL. Usually 75-80% of circulating cells are lymphocytes'. – CMDT*
  ***The patient in question is presenting with a white cell count of 100,000/mcL and 80% of circulating cells are lymphocytes. This finding is consistent***

**252. Answer is D (T lymphocyte CLL is more common):** Harrison 18th/p 926, 927 *Harrison 17th/693; Clinical Malignant Hematology 1st (2007)/254*

*The most common form of CLL is a B-cell CLL.*

**The most common form of Chronic Lymphocytic leukemia is a B-cell CLL**
*B cell CLL is more common than T cell CLL.*

**CLL is diagnosed on routine blood tests/Leukocytosis**
Typical (B cell) CLL is often found incidentally when a complete blood count is done for another reasons.
*The diagnosis is usually made when an increased number of circulating lymphocytes (↑WBC count) is found on routine complete blood counts.*

**CLL does not normally present as an acute Leukemia**
Transformation of CLL into acute Leukemias has been reported in a few studies but such transformation is extremely rare, and there is no convincing evidence that CLL ever transforms into an Acute Leukemia.

*'There is no convincing evidence that CLL ever transforms into ALL' – Clinical Malignant Hematology 1st (2007)/254*

**253. Answer is C (CLL) :** Harrison 18th/p 919, 921 *Harrison 16th / 648; Harrison 17th/ 687, 691; API 8th/901; CMDT 2006 / 510; 2009/454-455*

***Incidental finding of Lymphocytosis (80,000/mcL) in an elderly and asymptomatic patient suggests the diagnosis of CLL.***

***Why is CLL the single best answer of choice here ?***

- *'CLL is a disease of older patients wth 90% of cases occurring after the age of 50 years and median age of presentation is 65 years'. – CMDT*
  ***The patient in question is aged 80 years and hence falls in the bracket of CLL.***
- *'Typical B cell CLL is often found incidentally when a complete blood count is done for another reason'. – Harrison 16th / 648*
  ***The patient in question is asymptomatic and the findings represent incidental observation on a full blood count done for an obscure reason.***
- *'The hallmark of CLL is absolute lymphocytosis. White cell count is usually greater than 20,000/mcL may be markedly elevated to several 100,000/mcL. Usually 75-80% of circulating cells are lymphocytes'. – CMDT*
  ***The patient in question is presenting with a white cell count of 100,000/mcL and 80% of circulating cells are lymphocytes. This finding is consistent with the blood picture of CLL.***

**254. Answer is D (t(11,14) translocation is present in most of the cases):** Harrison 18th/p 923 *CMDT 2008/449; Washington manual of oncology 2nd/325; Postgraduate Hematology 4th/627; Robbins 7th/674; Harrison 17th/690; Wintrobe's 11th/2434*

*The profile of this patient is consistent with a diagnosis of CLL (Refer previous question)*

***t (11;14) translocation is characteristic of Mantle cell lymphoma and not CLL. The most common genetic abnormality in CLL are deletions on the long arm of chromosome 13 (13q14)***

Genetic Abnormalities in CLL and Associated Prognosis

| Genetic Abnormalities with good Prognosis | |
|---|---|
| 13q14 deletion | Good Prognosis<br>***Long term survival*** |

| Genetic Abnormalities with poor prognosis | |
|---|---|
| Chromosome 11 deletion (11q22-23 deletion) | • Poor prognosis<br>• Younger age<br>• ***Bulky lymphadenopathy***<br>• Reduced survival |
| Chromosome 17 detection (17 p 21 detection) | • Poor Prognosis<br>• Poor Response to therapy<br>• Transformation |
| Chormone 12 Trisomy (Trisomy 12) | • Poor prognosis<br>• Atypical morphology<br>• ***Aggressive course/Progressive***<br>• High proliferation rate |



**255. Answer is A (A pseudofollicular pattern with proliferation centres):** *William's 7th/1347; Hoffman's 4th/1381; Robbins 7th/673,674; Handbook of Human Immunology 2nd/245*

*Coexpression of CD19 and CD 5 together with negative CD 79 and FMC7 markers suggest a diagnosis of chronic lymphocytic leukemia (CLL)*

***The histapathological examination of lymph nodes in CLL shows characteristic effacement of normal nodal architecture by diffuse proliferation and infiltration of small round lymphocytes (and not medium to large lyumphocytes). Pseudofollicular growth centres or proliferation centres are present in most cases and when present proliferation centres are considered pathognomic of CLL/SLL***

Approach to the question

What is the diagnosis of the patient in question?
The patient in question is case of CLL

*CLL is characterized by coexpression of CD5 and CD19Q*
*CLL is characteristically positive for CD23 and usually negative for CD7/9b and FMC7Q*

| Lymphoma | CD5 | CD19 | CD20 | CD23 | CD79b | FMC7 |
|---|---|---|---|---|---|---|
| CLL | + | + | +/- | + | - | - |

What are the histopathological characteristics of CLL?
Histopathological Features of CLL *(Robbins/Williams/Haffman)*

- *Lymph nodes in patients with CLL characteristically are diffusely infiltrated with monomorphic small round lymphocytes that efface the normal node architecture*

  ***Diffuse effacement by a predominant population of small lymphocytes***

- *The predominant cell is a small lymphocyte with clumped nuclear chromatin.*

  These cells may be mixed with variable number of larger cells called prolymphocytes, but the predominant cells remain small lymphocytes.

- *Pseudofollicular growth centres or proliferation centres are present in most cases.*
  *Proliferation centres are clusters of prolymphocyte appearing cells that form aggregates or pseudofollicles, and so called because they contain a large number of mitotically active cells.*

  ***When present proliferation centres are considered pathognomic of CLL/SLL-****Robbins 7th/673*

**256. Answer is B (Chronic Lymphocytic Leukemia):** *CMDT' 2006/510;2008/449; 2009/455; Refer previous question*

*Coexpression of the B Lymphocyte lineage marker CD 19 and the T lymphocyte marker CD 5 is unique to CLL and Mantle cell Lymphoma.*

*CD 23 is expressed by CLL and not by Mantle cell Lymphomas.*
***CLL cells are also negative for CD 79B and FM 7 and hence CLL is the answer of choice.***

| | CD5 | CD9 | CD23 |
|---|---|---|---|
| Mantle cell Lymphoma | ++ | ++ | +-/+ |
| CLL | ++ | ++ | ++ |

*Mantle cell Lymphoma also tend to express higher levels of CD79a and CD79b than CLL.*

**257. Answer is A (Large B cell lymphoma):** *Robbins & Cotran Pathologic Basis of Disease 9TH/ 594*

***Richter syndrome or Richter transformation refers to the transformation of CLL/SLL into an aggressive Diffuse Large B-Cell Lymphoma (DLBCL).***

**258. Answer is A (Treatment should be initiated as soon as diagnosis is established):** *Harrison's 18th/ 927,928; Oxford Desk Reference: Oncology (Oxford University Press, 2011)/ 482; DeVita, Hellman, and Rosenberg's Cancer: Principles & Practice of Oncology (2008)/ 2283*

***It is not essential to initiate treatment as soon as a diagnosis of CLL is established.***

*'An unusual feature of CLL compared to other leukemias is that making the diagnosis is not necessarily an indication to initiate treatment' – DeVita*

**Treatment need not be initiated as soon as diagnosis of CLL is established**

*Early stage asymptomatic disease requires no treatment. CLL may be diagnosed in an asymptomatic patient and have a prolonged course. Meta-analysis has shown no survival advantage of initiating treatment in early stage disease. Active monitoring should however be pursued and treatment initiated only if and when the patient meets established 'criteria for treatment'.*

| Criteria for treatment |
|---|
| • Progressive marrow failure |
| • Massive(>10cm)/progressive lymphadenopathy |
| • Massive (>6cm)/progressive splenomegaly |
| • Progressive lymphocytosis (doubling time <6 months) |
| • Systemic symptoms; |
| • Weight loss >10%in 6 months fever>38° C for >2 weeks extreme fatigue or night sweats |
| • Autoimmune cytopenias (this may only require treatment of the autoimmune component not necessarily the leukaemia) |

**Chlorambucil and Fludarabine are the most commonly used agents.**

*The most common treatment for CLL are Chlorambucil or Fludarabine alone or in combination.*

| *Chlorambucil* |
|---|
| • *Can be administered orally and has few side effects* |
| • *Less active than Fludarabine and usually unsuccessful in achieving remission* |
| • ***Most common agent chosen for treatment of elderly patients requiring therapy.*** *(Majority of elderly patients have significant comorbid conditions associated with aging and may have an indolent disease )* |

| *Fludarabine* |
|---|
| • *Administered intravenously and has significant side effects (Significant immune suppression)* |
| • *More active agent and by far the only drug associated with a significant incidence of complete remission* |
| • ***Preferred agent for treatment of young patients requiring therapy*** *Fludarabine is often used in combination with Cyclophosphamide (FC).Following the results of LRF CC4 Trial many now consider FC to be the gold standard first Line treatment of CLL in the young* |

***Bendamustine*** *is an alkylating agent structurally related to nitrogen mustards that is highly effective and is vying with fludarabine as the primary treatment of choice.*
***Rituximab*** *(AntiCD20) and* ***Alemtuzumab*** *(anti CD52) may also be used.*

**Young patients are candidates for Bone marrow transplanatation**

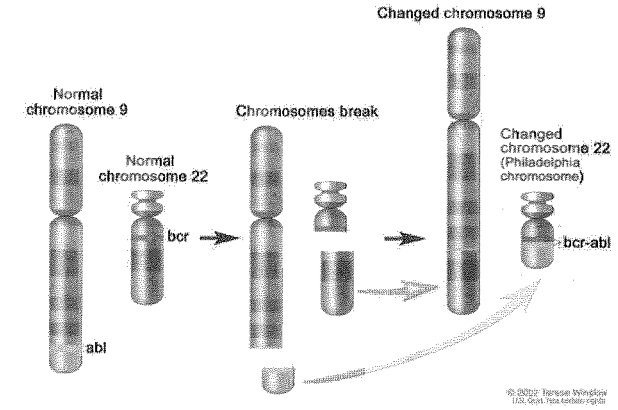
*'Young patients with CLL can be candidates for Allogenic bone marrow transplantation. Allogenic bone marrow transplantation can be urative but is associated with a significant treatment related mortality rate' – Harrison*

## Chronic Myeloid Leukemia (CML) and CMML

**259. Answer is D (The Philadelphia chromosome with the oncogenic BCR-ABL gene is found on chromosome 9):** *Multiple references*

***The Philadelphia chromosome with the oncogenic BCR-ABL gene fusion is the truncated chromosome 22 (and not chromosome 9).***

- The Philadelphia chromosome results from a reciprocal translocation between the ABL-1 oncogene on the long arm of chromosome 9 (region q34) and the breakpoint cluster region (BCR) on the long arm of chromosome 22(region q11)
- This reciprocal translocation, creates an elongated chromosome 9 (der 9), and a truncated chromosome 22. The oncogenic BCR-ABL gene fusion is found on the shorter derivative 22 chromosome (Philadelphia Chromosome).
- BCR-ABL encodes an oncogenic protein with tyrosine kinase activity (Tyrosine Kinase Inhibitors are therefore used for treatment)
- In agreement with the International System for Human Cytogenetic Nomenclature (ISCN), this chromosomal translocation is designated as t(9;22)(q34;q11). ABL stands for "Abelson", the name of a leukemia virus which carries a similar protein.




**260. Answer is C (Chronic myelogenous leukemia):** *Harrison 18th/ p915 CMDT 2008/444; CMDT 2009/449; Harrisons 17th/684*

***Peripheral blood picture with excessive number of granulocytes, basophills and eosinophils is characteristic of chronic myeloid leukemia (CML). CML is also often associated with an elevated platelet count (thrombocytosis) sometimes to strikingly very high levels. Chronic myelocytic leukemia is the single best answer of choice.***

CML

Chronic myeloproliferative disorder from neoplastic transformation of a bone marrow stem cell that still retains capacity to differentiate along erythrocytic, megakaryocytic and granulocytic or monocytic lines.

**Pripheral blood picture**

- Striking Leucocytosis (Elevated WBC count)
  Both immature and mature farms in different Stages of maturation may be seen But
  ***Blood picture is dominated by Mature forms and precursor in the intermediate stages of differentiation***
  (Neutrophils, Metamyelocytes and Myelocytes)

  **Immature forms are less numerous**
  Blasts <5%
  Promyelocytes <10%

  (Cells are usually present in direct degree to the stage of maturation)

  **Basophills Eosinophils may be increased**
  - Elevated Basophils (often present)
  - Elevated Eosinophils (less common)
- **Thrombocytosis**
  Elevated platelet count if often present. Platelet count may be normal or sometimes elevated to strikingly high levels
- **Erythrocytes**
  Red blood cell morphology is normal.
  Patient is usually not anemic or only mildly anemic

**Bone marrow**

- Bone marrow is hypercellular with left shifted myelopoesis
- Myeloid: Erythroid ratio is increased
- Myeloblasts comprises less than 5% of marrow cells

**Special Tests**

- Cytogenetic Analysis for Philadelphia Chromosome
  A small chromosome 22 caused by t (9; 22) translocation that results in bcr/abl fusion gene
- Reduced Leukocyte alkaline phosphatase levels (↓LAP)
  This indicates that although the total number of granulocytes is increased they are functionally impaired
- Serum levels of vitamin $B_{12}$ proteins is ↑ed binding.

**261. Answer is B (t (9; 22):** Harrison 18th/p 915 *CMDT 2008/444; CMDT 2009/449; Harrisons 17th/684; Refer previous question*

***The patient in question is a case of chronic myeloid leukemia (CML)***
***And the characteristic cytogenetic abnormality in CML is the t (9; 22) translocation resulting in the Philadelphia chromosome***
*The diagnosis of CML is suggested by the characteristic laboratory feature (strikingly elevated WBC count with mature forms dominating the picture, associated basophilia and less that 5% blasts and promyelocytes) and supported by the clinical features (non specific symptoms of fatigue and weight loss along with heaviness in left hypochondrium suggesting massive splenomegaly which is characteristic of CML)*

**Cytogenetic Abnormality in CML**

- CML is characterized by a reciprocal translocation between chromosome 9 and 22 t (9:22)
- This translocation results in the fusion of BCR gene on chromosome 22 with ABL gene (protoncogene) located on chromosome 9 forming the BCR-ABL fusion gene

  The abl gene on chromosome 9 is translocated to bcr site on chromosome 22

- The bcr-abl gene is the hallmark of CML and may be detected in peripheral blood

  Refer previous question for characteristic laboratory findings in CML

**Clinical Presentation in CML**

Clinical Presentation
(Presenting features)

**Common presenting features**

| Asymptomatic | Non specific symptoms | Symptoms from splenomegaly |
|---|---|---|
| Discovered incidentally during health screening tests | • Fatigue<br>• Malaise<br>• Weight loss | • Early satiety<br>• Left hypochondrial heaviness or left upper quadrant pain<br>*(CML is associated with massive splenomegaly)*[Q] |

Physical examination : Physical signs
- Splenomegaly (mild, moderate, massive), and sternal tenderness are characteristic
- Mild hepatomegaly may be present & lymphademopathy is unusual

**Uncommon presenting features**

| Features related to Granulocyte /Platelet dysfunction |
|---|
| • *Infection*<br>• *Thrombosis*<br>• *Bleeding* |

| Leukostatic manifestations d/t severe Leukocytosis or thrombosis |
|---|
| • *Vasoocclusive disease*<br>• *Corebrovascular accidents*<br>• *Myocardial infarction*<br>• *Venous thrombosis*<br>• *Priaprism*<br>• *Visual disturbance*<br>• *Pulmonary insufficiency* |

**262. Answer is A and B (Accelerated phase and Blast crisis):** Harrison 18th/p 915 *Refer text below; Harrison 17th/684; manual of Clinical Oncology 5th/504*

*The natural history of CML is a triplastic process. Most patients present in a chronic phase and may progress to an accelerated phase or blast phase.*
*'Evolution of accelerated or blast phase from the chronic phase is suggested by the* ***development of anemia,*** *thrombocytopenia, leukocytosis with immature myeloid cells or basophilia,* ***increasing splenomegaly*** *or recurrent contiutional symptoms while on therapy'. – Manual of Clinical Oncology 6th/504*

**263. Answer is D (Persistant thrombocytosis > 1000 x $10^9$/L positive to therapy):** *Harrison 17th/ 684; API 7th/957*

***Accelerated phase is associated with thrombocytopenia (<100 x $10^9$/L) and not thrombocytosis.***

*Although multivariate analysis derived criteria also place blood or marrow basophils > 20% in disease criteria, other criteria do consider marrow and peripheral basophills > 10% as a criteria and hence option (D) is the single best answer here.*

***Accelerated phase of CML*:** It is defined by the development of increasing degrees of anemia unaccounted for by bleeding or chemotherapy and is defined by several criteria.

| Multivariate analysis derived criteria | Other commonly used criteria |
|---|---|
| Cytogenetic clonal evolution | *Splenemegaly unresponsive to therapy* |
| *Blood or marrow blasts between 10 and 20%* | Increasing drug dosage requirement |
| ***Blood or marrow basophills > 20%*** | Marrow reticulum or collagen fibrosis |
| *Platelet count < 100 x $10^9$/L unrelated to therapy* | Marrow or peripheral blasts > 10% |
| | *Marrow or peripheral basophills ± eosinophills ≥ 10%* |
| | Triad of WBC > 50 x $10^9$/L, hematocrit < 25% and |
| | *platelets < 100 x $10^9$/L not controlled with therapy* |
| | Unexplained fever or bone pain |

**264. Answer is B (CML):** Repeat

***Leucocyte alkaline phosphatase is characteristically low in chronic myeloid leukemia.***

| Leucocyte Alkaline phosphatase is decreased in |
|---|
| • **CML** (chronic myeloid leukemia) |
| • **PNH** (Paroxysmal nocturnal hemoglobinuria) |

**265. Answer is A (Size of splenomegaly indicates prognosis):** Harrison 18th/p 915 *Harrison16th/638;17th/683,684; Chandrasoma Taylor 3rd/ 420*

- ***Splenomegaly or size of enlarged spleen is used as a prognostic indicator in CML as part of the 'Sokal index'.***

| **Sokal index: Prognosis in CML** – *Harrison 15th/ 712* |
|---|
| 1. % of Circulating blasts |
| 2. Spleen size |
| 3. Platelet count |
| 4. Age |
| 5. Cytogenetic clonal evaluation |

- In CML, the dominant cell lines in the peripheral blood and bone marrow are – myelocytes, metomyelocytes and granulocytes.

  The Philadelphia chromosome is present in all these cell lineages and *remains detectable even after remission of the CML – Chandrasoma Taylor 3rd/ 420.*

- Phagocytic functions are usually normal at time of diagnosis and remain normal during the chronic phase-*Harrison 15th/ 711*

| **Remember** |
|---|
| • $\mathcal{Q}$ Leucocyte alkaline phosphatase is characteristically Low $\mathcal{Q}$ in CML. |
| • $\mathcal{Q}$ Serum levels of vit $B_{12}$ and vit $B_{12}$ binding proteins are $\uparrow^{ed}$ $\mathcal{Q}$ |

- Myeloblastic cells are Sudan black positive.

**266. Answer is C (Philadelphia chromosome is positive) :** *Ghai 5th / 465*

***Juvenile CML is mostly seen in children below 2 years of age. Philadelphia chromosome is negative and leukocyte count is less than 100'000/mm3.– Ghai***

| Features | Adult CML | Juvenile CML |
|---|---|---|
| • Age | - 10-12 years | - < 2 years |
| • Bleeding manifestation | - Absent | - Frequent |
| • ***Thrombocytopenia*** | - Uncommon | - Frequent |
| • Rash | - Absent | - Frequent |
| • ***Lymphadenopathy*** | - Rare | - Frequent |
| • Splenomegaly | - Marked | - Variable |
| • WBC count at diagnosis | - > 100'000 | - < 100'000 |
| • WBC type | - Granulocyte | - Monocyte |
| • Normoblastic | - Unusual | - Common |
| • ***HbF*** | - Normal | - Increased |
| • Immunoglobulins | - Normal | - Increased |
| • Muramidase levels | - Normal | - Increased |
| • Response to Busulphan | - Good | - Poor |
| • Survival | - 2.5-3 years | - 9 months |

**267. Answer is A (Juvenile CML):** *Ghai 6th/569; Other texts*

***Fetal haemoglobin (HbF) values are elevated in most cases of juvenile CML – Ghai 6th/569***

**HbF is raised in following conditions**
- *Juvenile CML*[Q]
- β thalossemia[Q]
- Sickle cell anaemia[Q]
- Heriditary persistence of fetal haemoglobin (HPFF)

**268. Answer is A (Juvenile CML):** *Ghai 6th/759; Wintrobe's Hematology 14th/ 108*

***Fetal Haemoglobin Levels (HBF) are typically increased in Juvenile CML.***

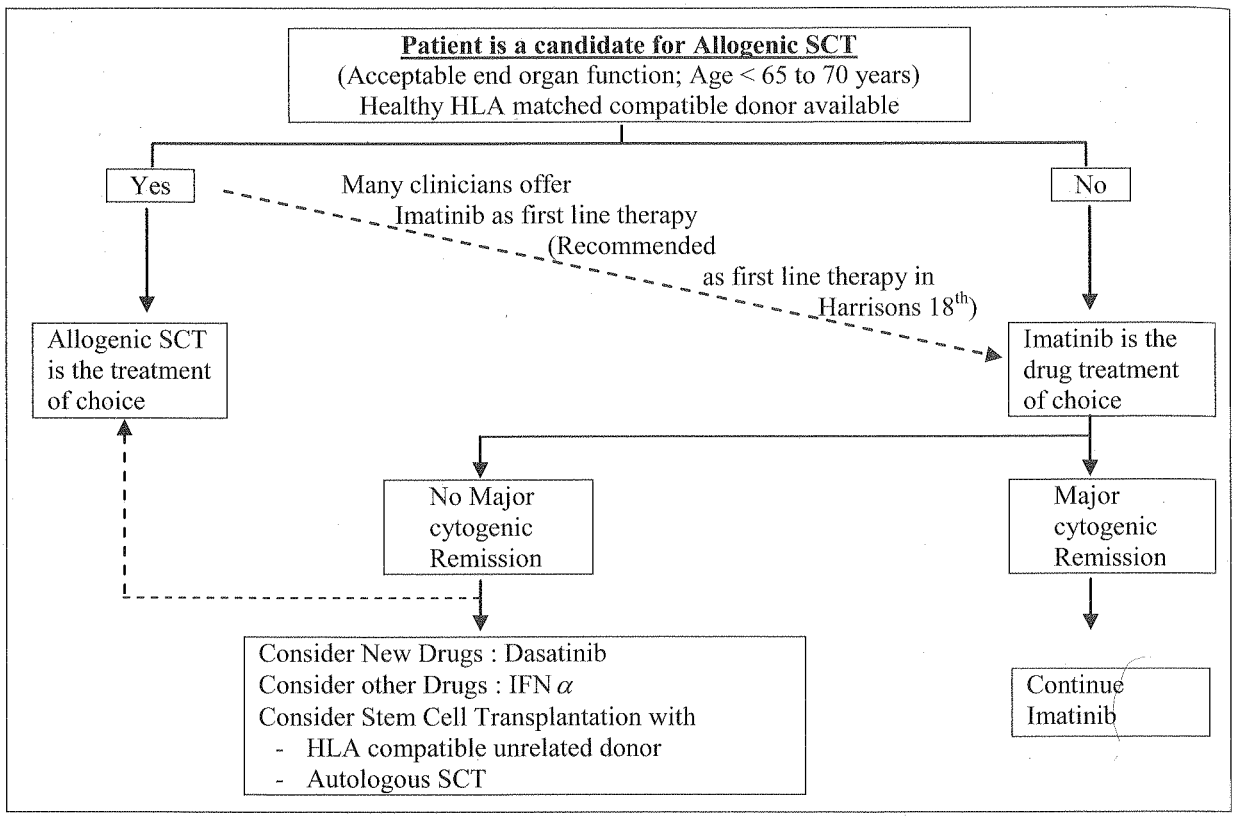
**269. Answer is B (Imatinib Mesylate Therapy):** *Harrison's 18th/915*

***Harrison's 18th edition recommends starting treatment of newly diagnosed CML with TK inhibitors (Imatinib) and reserving alloginic transplantation for those who develop Imatinib resistance.***

*'The therapy of CML is changing rapidly because we have a proven curative treatment (allogenic transplantation) that has significant toxicity and a new targeted treatment (imatinib) with outstanding outcome based on 8 year follow up data. We recommend starting with TK inhibitors (Imatinib) and reserving allogenic transplantation for those who develop imatinib resistance' -Harrison's 18th*

**Note:**
- *The only curative treatment for CML is Allogenic stem cell Transplntation*
- *The treatment of choice in CML is Allogenic BMT*[Q]
- *The drug treatment of choice in CML is Imatinib*[Q]
- *Initial treatment recommended for newly diagnosed patient with CML is Imatinib.*

**Treatment of CML**
- The only curative treatment for CML is Allogenic Stem Cell Transplantation (SCT) (Allogenic bone marrow transplantation)[Q]
- The treatment of choice for CML is also Allogenic Stem Cell Transplantation (SCT) (Allogenic bone marrow transplantation)[Q]
- ***The drug treatment of choice for CML is Imatinib*** [Q]
- *Interferon alpha (IFN α ) used to be the drug treatment of choice for CML when Imatinab was not available*




**270. Answer is A (Imatinib):** *Harrison's 18th/ 915*

***Tyrosine Kinase Inhibitors (Imatinib) are the chemotherapeutic agents for choice in the management of CML.***
*Tyrosine Kinase inhibitors target the 'constitutively active tyrosine kinase' implicated in the pathogenesis of CML. Although they do not cure the disease, these agents are able to achieve long term control of CML in the majority of patients. Most recent texts (Including Harrisons) recommend Tyrosine Kinase Inhibitors (Imatinib) as the initial treatment of choice for newly diagnosed CML reserving Allogeneic Stem Cell Transplantation (SCT) for those who develop Imatinib Resistance.*

**271. Answer is B (Imatinib):** *Harrisons 17th; CMDT 2008/444; CMDT 2009/450*

***Imatinib mesylate is the drug of choice for management of Chronic Myeloid Leukemia.***

**272. Ans. Answer is A (Imatinib):** *Harrison 17th /685; Harrison's 18th/915*

***The drug of choice for drug treatment of CML is Imatinib mesylate.***

**273. Answer is B (Allogenic BMT):** Harrison 18th/p 915 *Harrisons 17th/685; CMDT 2008/444; CMDT 2009/450*

***The only curative treatment for CML is Allogenic stem cell Transplntation***

**Note:**
- *The treatment of choice in CML is Allogenic BMT*
- *The drug treatment of choice in CML is Imatinib*

**274. Answer is C (More than 20% blasts in blood or bone marrow):**
*Wintrobe's atlas of clinical hematology 1st (2006) /133,134*

***Chronic myelomonocytic leukemia (CMML) is characterized by less than 20% blasts in peripheral blood or bone marrow.***

**Diagnostic Criteria for Chronic Myelomonocytic Leukemia according to WHO**

- It is a chronic disorder (a variant of C.M.L)
- Middle aged and elderly males are usually affected
- ***Persistent peripheral blood monocytosis is >1×10$^9$/L.***
- Absence of Philadelphia chromosome or BCR/ABL rearrangement
- ***Blasts are less than 20% in peripheral blood or bone marrow.***
- Dysplasia in one or more myeloid lineages, or ***in the absence of dysplsia, CMML can be diagnosed***, if all other criteria are met together with either of the following
  - Presence of clonal cytogenetic abnormality
  - Monocytosis has been persistent for at least 3 months and all other causes of monocytosis have been excluded.

CMML must after be differentiated from CML and atypical CML

| | CGL (CML) | aCML | CMML |
|---|---|---|---|
| Basophils | >2% | <2% | <2% |
| Monocytes | <3% | >3-10% | >3-10% usually |
| Granulocyte dysplasia | - | ++ | + |
| Immature granulocytes | >20% | 10-20% | <10% |
| Blasts | <2% | >2% | <2% |

## Mycosis Fungoides

**275. Answer is C (Indolent course and easily amenable to treatment) :**
*Harrison 18th/p 932; 16$^{th}$ / 653; 17$^{th}$/ 697; Robbins 7$^{th}$ / 1250; CMDT 2006 / 106; CMDT 2008/ 102; CMDT 2009/108*

***Although Mycosis fungoides has an indolent course it is not easily amenable to treatment.***

**Mycosis Fungoides**

Mycosis fungoides is synonymous with Cutaneous T cell lymphoma.

**Clinical presentation and course :**

- Mycosis fungoides ***has an indolent course.***
  *Most affected individuals have disease that remains localized to the skin for many years.*
  *It begins on the skin and may involve only the skin for years or decades*
- Presentation is with localized or generalized erythematous / eczematous skin lesions.
  Skin lesion progress from 'patch' stage to 'plaque stage' to cutaneous 'tumors' stage.
- Metastasis occurs in advanced stages :

| To lymph nodes | Peripheral circulation |
|---|---|
| | ***Sezary syndrome (Erythroderma and Circulating tumor cells)*** Seeding of the blood by melanoma cells is accompanied by diffuse erythema and scaling of the entire body surface (erythroderma). |

**Histology**

| Sezary - Lutzner cells | ***Pautrier Microabscesses*** |
|---|---|
| • Histological hall mark of Mycosis fungoides<br>• These are T helper cell (CD4 positive) | Sezary - Lutzner cells characterstically form band like aggregates within the superficial dermis and invade the epidermis as single cells or small clusters called Pautrier's Microabscesses. |

**Treatment (Mycosis fungoides is not easily amenable to treatment)**

- ***The treatment of Mycosis fungoides is complex. Even early and aggressive treatment has not been proved to cure or prevent progression of the disease.*** *-CMDT*
- *Cure has been possible with radiotherapy only in rare patients with early stage mycosis fungoides.*
- *Most of the treatment for mycosis fungoides are 'palliative'.*

## Acute Leukemia

### General Characteristics

**276. Answer is A (CD 19) :** *Robbins 7th/670; Blood by Handin Lux and Stossel 2nd/46*

***CD 19 is a marker for B lymphocytes.***

**Markers for various lineage**

**Lymphoid lineage**

| B Lineage | T Lineage |
|---|---|
| *CD79a* | *CD3 (m/cyt)* |
| *cyt IgM* | *Anti-TCR α/β* |
| *cyt CD22* | *Anti-TCR γ/δ* |
| ***CD19*** | *CD2* |
| *CD10* | *CD5* |
| *CD20* | *CD8* |
| | *CD10* |
| *TdT* | *TdT* |
| *CD24* | *CD7* |
| | *CD1a* |

**Myeloid lineage**

| Myeloid Lineage |
|---|
| *Anti-MPO (monoclonal)* |
| *MPO cytochemistry* |
| *CD117* |
| *CD13* |
| *CD33* |
| *CD65s* |
| *Anti-MPO (polyclonal)* |
| *CD14* |
| *CD15* |
| *CD64* |

**277. Answer is A and B (CD2 and CD3):** *Robbins 7th/670: Refer previous question; Medical Immunology 5th/179*

***CD2 and CD3 are pan T cell markers.***

**Important Tcell markers**

| Pan Tcell markers | Subset Markers |
|---|---|
| *Markers that are common to all cells of a given type* | *Markers that are present only on a subset of population of cells in a given lineage* |
| Pan T cell markers include | Subset T cell markers include |
| ***CD2*** | *CD4* |
| ***CD3*** | *CD8* |
| *CD5* | |
| *CD7* | |

*Note that their specificity is not absolute because CD2 is also expressed by NK cells and CD3 by a special subpopulation of NK cells.*

**278. Answer is D (MPO):** *Refer previous question*

***MPO (myeloperoxidase) is a marker for myeloid lineage***

Important Marker for Myeloid lineage

AntiMPO (monoclonal)
MPO cytochemistry
CD117
CD13
CD33
CD65s
Anti-MPO (polyclonal)
CD14
CD15
CD64

**279. Answer is D (CD 45RO):** *Harrison 15th/1808*

| CD Marker | T cell |
|---|---|
| CD 45 RA | subset T, medullary thymocytes "naïve" T cells |
| CD 45 RB | All leukocytes |
| CD 45 RC | subset T, medullary thymocytes, "naïve" T cells |
| CD 45 RO | subset T, cortical thymocytes, **"memory"** T cells |

**280. Answer is D ( t(9; 20): ALL):** *Harrison 17th / 690; Chandrasoma Taylor 3rd /296; Robbins 7th /314*

***Acute Lymphoblastic leukemia (ALL) may be associated with t(4;11), t(9;22) or t(8; 14) but association with t(9; 20) is not seen.***

| Type of Leukemia | Translocation | Deletion (-) / Trisomy (+) |
|---|---|---|
| Chronic myelocytic leukemia (CML) | t(9; 22)[1]Philadelphia chromosome | - |
| Acute Myoblastic Leukemia (AML) | t(8; 21), t(9;22) | +8, 7-, 5-, 7q, 5q- |
| Acute Monocytic Leukemia | t(9; 11), t(11; 23) | - |
| Acute Promyelocytic leukemia (M3) | t(15; 17) | |
| Acute lymphoblastic leukemia (ALL) | t(4; 11), t(9; 22), t(8; 14) | 20q- |
| Chronic lymphocytic leukemia (CLL) | - | +12 |
| Erythroleukemia | - | 7q-, 5q- |
| Polycythemia Rubravera | - | 20q- |

## Acute Lymphoid Leukemia (ALL)

**281. Answer is A (Pre-B cell ALL):** Harrison 18th/p 919 *Harrisons 17th/687*

***Pre B-cell ALL are the commonest types of Acute Lymphoplastic leukemias and account for upto 75% of all ALL***

Classification of Acute Lymphoid Leukeia (ALL)

| Immunologic Subtype | % of Cases | FAB Subtype | Cytogenetic Abnormalities |
|---|---|---|---|
| Pre-B ALL | 75 | L1, L2 | t(9;22), t(4, 11), t(1; 19) |
| T Cell ALL | 20 | L1, L2 | 14q 11 or 7q34 |
| BCell ALL | 5 | L3 | t(8; 14), t(8; 22), t(2;8) |

**282. Answer is C (ALL):** *Harrison 18th/p 932; CMDT 2008/447; Robbins 7th/670; NMS Rediatrics 4th/533,534*

***The presence of a mediastinal mass is a characteristic feature of 'T' cell ALL.***

*'Precursor T cell ALL is most often found in young men presenting with a large mediastinal mass' – Harrison*

*A young adolescent male presenting with a mediastinal mass is most often a precursor T cell ALL.*

**Characteristic Features of T cell ALL (20% of ALL)**

- *Occurence in older children (adolescents) and adults*
- *Predilection for males*
- *Presence of anterior mediastinal mass in upto half of the cases at presentation (thymic mass)*
- *Early central nervous system involvement*
  *-(Early dissemination to meninges and testes)*
- *High WBC count often greater than 100,000/mm$^3$*

**283. Answer is B (An immature T cell phenotype-Tdt/CD34/CD7 positive):** Harrison 18th/p 932 *CMDT 2009/452, 453 Harrisons 17th/697; Blood by Hadden & Stossel 1st/44*

***The presence of a mediastinal mass in a young adolescent male suggests the diagnosis of precursor T cell ALL. Precursor T cell ALL is phenotypically characterized by an immature T cell phenotype and is positive for TDT and CD7 and may be positive for CD34.***

**The patient in question has a Tcell ALL (Precursor T cell ALL)**

***Patient is presenting with characteristic clinical features of T cell ALL***

- *Occurance in an adolescent age group (17 year old)*
- *Occurance in a male (predilection for males)*
- *Presence of a mediastinal mass*
- *High WBC count > 100,000/mm3*

**Presursor T cell ALL will show an immature T cell Phenotype and will be positive for CD7 and Td t**

Immunophenotypic classification for ALL

| FAB classification | Immunologic classification | Phenotype | Incidence (% cases) | | Cytogenetic Abnormalities |
|---|---|---|---|---|---|
| Pre-B Cell | Early Pre-B | CD19, CD20-/+, CD10, CD34, TdT | 55 | 75 | t(9;22), t(4, 11), t(1; 19) |
| | Pre-B | CD19, CD20+/-, CD10, CD34-, cIgM, Tdt+/- | 20 | | |
| B cell | B cell | CD19, CD20, CD22, CD10+/-, CD34-, Tdt-, sIg | 5 | | 14q 11 or 7q34 |
| T cell | T cell | CD1, CD2, CD3, CD5, CD7, CD10+/-, CD34-/+, Tdt, dual CD4/CD8 | 20 | | t(8; 14), t(8; 22), t(2;8) |

**284. Answer is C (Pre B cell ALL):** *Devita 6th/2240, 2237; Nelson 17th/1695; Ghai 6th/563; Harrison 16th ; Wintrobe's 11th/2145, 2142; Hoffman 4th/1159*

*Hyperdiploidy, Female sex and translocation t (12, 21) are associated with good prognosis.*
*Pre B cell ALL may be associated with a poor prognosis and is the single answer of exclusion.*

**Hyperdiploidy Female sex and translocation t (12, 21) are associated with good prognosis.**

**Prognostic factor for ALL:**

| **Determinants** | **Favourable** | **Unfavrourable** |
|---|---|---|
| White blood cell count | Low WBC count* | High WBC count* |
| ***Age*** | ***3-7 yrs*** | ***<1, > 10 yr*** |
| Gender | Female | Male |
| Ethnicity | White | Black |
| Node, Liver, spleen enlargement | Absent | Massive |
| ***Testicular enlargement*** | ***Absent*** | ***Present*** |
| Central nervous system leukemia | Absent | Overt (blasts + pleocytosis) |
| FAB morphological features | L1 | L2 |
| Ploidy | Hyperdiploidy | Hypodiploidy < 45 |
| DNA index | > 0.16 | < 0.16 |
| Cytogenenetic markers | Trisomies 4, 10 and/or 17<br>t(12;21) (tel aml 1) | t(9; 22) [bcr abl]<br>t(4; 11) [mll af4]<br>t(1; 19) |
| Time to remission | < 14 d | > 28 d |
| Minimal residual disease | $< 10^{-4}$ | $> 10^{-3}$ |
| Immunophenotype | Early Pre-B cell | T cell |

**Pre B cell ALL is often associated with an unfavourable prognosis (although it may be associated with a favourable outcome)**

Pre B cell ALL has been associated with a poorer outcome compared to Early Pre B cell ALL. – *Wintrobe's*

Immunophenotype and Prognosis

| Early Pre B cell ALL | Pre B cell ALL | Mature B cell ALL | T cell ALL |
|---|---|---|---|
| Early Pre B cell All comprises about 2/3 cases of childhood ALL and is associated with a favourable prognosis.<br>*Most Early Pre B cell ALL are CALLA positive. CALLA expression does not appear to have independent prognosis significance.* | Pre B cell ALL account for 20% of childhood ALL and have ***been associated with a poorer outcome compared to Early Pre B cell ALL.*** | Mature B cell ALL in uncommon in children and accounts for 1-2% of childhood ALL.<br>It is characterized by L3 FAB morphology ***and has a poor prognosis.*** | T cell ALL accounts for 15% of ALL in children<br>T cell ALL was (previously) ***associated with a poor prognosis*** but *recent use of more intensive therapeutic regimen has resulted in survival approaching that of Non T cell ALL.* |

**285. Answer is C (Pre B cell ALL):** *Devita 6th/2240, 2237; Nelson 17th/1695; Ghai 6th/563; Harrison 16th ; Wintrobe's 11th/2145, 2142; Hoffman 4th/1159; Refer previous question*

***Hyperdiploidy, Female sex and translocation t (12, 21) are associated with good prognosis.***

*Pre B cell ALL may be associated with a poor prognosis and is the single answer of exclusion.*

**286. Answer is C (Testicular involvement):** *Refer text below*

***Testicular involvement / enlargement is a typical poor prognostic factor for childhood ALL***

**Age < 2 years versus Testicular Involvement**

**Typically Age < 1 year is considered a poor prognostic factor**

*Although Age < 2 year has been mentioned as a poor prognostic factor in certain textbooks including Hoffman's Hematology (4th/1158) most textbooks use the criteria of Age < 1 year to define a poor prognostic factor*
*Since testicular involvement provided amongst the option is an established poor prognostic factor, this is selected as the single best answer of choice.*

**287. Answer is D (Hyperdiploidy):** *Hoffman 4th/1159; Wintrobe's 11th/2145, 2142*

***Hyperdiploidy is associated with a good prognosis***

**Hyperdiploidy is associated with a good prognosis**

*Patients with hyperdiploidy (>50 chromosomes) or DNA index > 0.16 have a favourable prognosis – Hoffman's 4th/1158*

**Age < 2 years has a poor prognosis**

*Patients who are very young (< 2 years) and older patients (> 10 years) tend to have a worse prognosis-Hoffman's 4th/1158*

*Although most textbooks use the criteria of Age < 1 year to define a poor prognostic factor, Age < 2 year has been mentioned as a poor prognostic factor in certain textbooks including Hoffman's Hematology (4th/1158)* ***Since Hyperdiploidy provided amongst the option is an established good prognostic factor, this is selected as the single best answer of choice.***

**High WBC count is associated with a poor prognosis**

*Initial leukocyte count at diagnosis has proved to be an important prognostic factor in virtually every ALL study. Different studies (textbooks) quote different values for the initial WBC count that is associated with a poor prognosis but uniformly a high WBC count carries a poor prognosis.*

| Different text books | Favourable WBC count | Unfavourable WBC count |
|---|---|---|
| *Wintrobe's Hematology* | *< 10,000* | *> 20,000* |
| *Hoffman Hematology* | *< 50,000* | *> 50,000* |
| *Manual of Clinical oncology* | *<30,000* | *>30,000* |
| ***Inference*** | ***Low WBC count*** | ***High WBC count*** |

**Male sex is associated with a poor prognosis**

*'Female patients have a rare favourable prognosis' – Hoffman 4th/1158*

**288. Answer is C (ALL):** *Ghai 6th/565*

***L- Asparginase is particularly used in treatment of ALL***

**289. Answer is A (Intrathecal methotrexate):** *Cancer Chemotherapy : Medicine outlinr series 2nd/167; Ghai 6th/564; Harrison 17th/1734*

***Intrathecal Methotrexate is the chemotherapy of choice for intracranial manifestation of Acute Leukemia***

**Treatment of choice for intracranial ALL**

***Combination of intrathecal methotrexate and cranial irradiation.***

| Agents used for Intrathecal chemotherapy |
|---|
| *Methotrexate* |
| *Cytarabine* |
| *Thiotepa* |

Note: Intrathecal Cytarabine may be as effective as intrathecal methotrexate

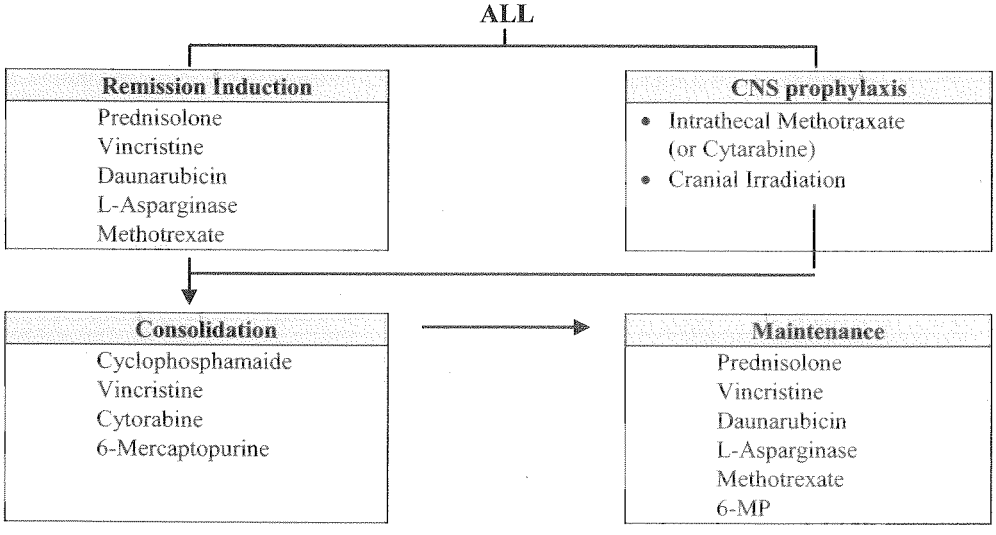
**290. Answer is A (ALL):** *Ghai 6th/564; Clinical Hematology and Oncology 1st (2003)/554, 560*

***Preventive treatment or CNS prophylaxis against the possibility of later central nervous system involvement is routinely administered in both children and adults with Acute Lymphoblastic Leukemia (ALL).***
*The concept of CNS prophylaxis in ALL is based on the fact that most children with ALL have subclinical CNS involvement at the time of diagnosis. The meninges harbour occult leukemic cells and act as a sanctuary site where leukemia cells are protected from systemic chemotherapy because of blood brain barrier.*

Note:
*CNS Relapse is very uncommon in AML.*

**291. Answer is B (All – trans-retinoic acid):** *Ghai 6th/565, 567*

***All – trans- retinoic acid is used in the treatment of M3 subset (Acute Promyelocytic leukemia) of Acute Myeloid Leukemia (AML) and not in ALL***




**292. Answer is A (Asparginase):** *Ghai 6th/563,564; Leukemia (Demos Medical Publishing, 2011)/267*

***L-Asparginase is one of the most important drugs in the treatment of both childhood and adult ALL***

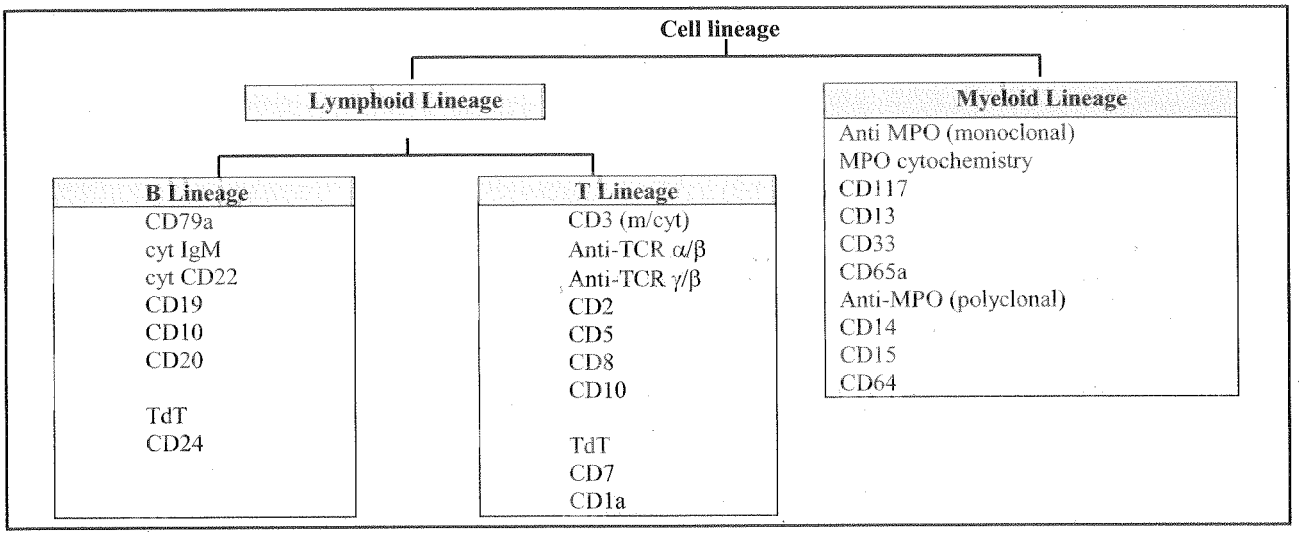
*L-asparagine is an amino acid that plays an essential role in protein. DNA and RNA synthesis and the survival of leukemic cells. L-Asparginase exerts its anti- leukemic activity by generating a state of relative L-Asparagine deficiency within blast cells. The usefulness of L-Asparginase therapy in Acute Lymphocytic Leukaemia (ALL) is more extensively documented in paediatric than in adult trials. Asparginase remains an important and universal component for the treatment of paediatric ALL and is being increasingly used for treatment of Adult ALL..*

**293. Answer is C (Acute lymphoblastic leukemia with hypereosinophilic syndrome):** *Refer text below*

*The immunophenotypic markers in the question are specific for lymphoid lineage alone and not for myeloid series.*

***Presence of immunophenotypic marker for myeloid lineage is essential before considering a diagnosis of biphenotypic leukemias, or Acute Eosinophilic leukemia (Eosinophils belong to the myeloid series) or Acute myeloid leukemia***
***The patient in question has positive markers for lymphoid series in isolation (CD19,CD10,CD20 and CD22) and hence the single answer by exclusion is Acute Lymphoblastic leukemia (lymphoid series) with hypereosinophilic syndrome.***

**Biphenotypic Acute Leukemia**
**Acute Eosinophilic leukemia**
**Acute myeloid leukemia** → *Diagnosis requires immunophenotypic markers of Myeloid lineage The patent in question stained negative for MPO and NSE and shows no positive markers for Myeloid lineage and hence a diagnosis of these malignancies can be excluded.*




**294. Answer is D (Inv (16) is often detected in the blasts and the eosinophils):**

*This is a case of ALL with hypereosinophillic syndrome. Inv (16) is associated with AML and not ALL, and therefore represents the incorrect statement amongst the option.*

**Abstract Title: Granular acute lymphoblastic leukemia with hypereosinophilic syndrome.**
**Journal Source**: Ann Hematol. 2000 May;79(5):272-4.
**Authors**: **Jain P, Kumar R, Gujral S, Kumar A, Singh A, Jain Y, Dubey S, Anand M, Arya LS.**
A four-year-old boy presented with marked peripheral blood eosinophilia (absolute eosinophil count of 54 x 10(9)/1), features of hypereosinophilic syndrome, and acute lymphoblastic leukemia (ALL-L2), the latter characterized by the presence of granular blasts. Blasts were negative for myeloperoxidase, non-specific esterase, acid phosphatase, periodic-acid Schiff stain, and toluidine blue. They exhibited an early pre-B immunophenotype (TdT, CD19, CD10, CD20 and CD22 positive) and stained negative for T (CD7, CD2, CD5 and CD3) and myeloid markers (MPO, CD33 and CD13). Chromosomal analysis revealed a normal karyotype. To the best of our knowledge, this case represents the first report of the coexistence of granular ALL and hypereosinophilic syndrome.

**Why ALL**

- Blasts were negative for myeloperoxidase and non specific esterase

| Type | Myeloperoxidase | Sudan black |
|---|---|---|
| AML | – | – |
| ALL | + | + |

- Presence of positive immunological markers CD 19, CD 20, CD 22 indicate a cell Lineage ALL

| Immunological markers for Bcell Lineage ALL: | CD19, CD 20, CD 22, CD 79a, cCD 22, cCD 79a |
|---|---|

**Why Hypereosinophillic Syndrome**: Option A Explanation

- Idiopathic hypereosinophillic syndrome is a rare condition characterized by extremely high levels of peripheral blood eosinophil counts. (80% of ($70 \times 10^9$) Leucocytes were eosinophils in this patient)
- Clinical picture of dry cough, dyspnea, wheezing etc is further suggestive of HES.
- *This is differentiated from eosinophillic leukaemia by the* ***absence of eosinophilic blast cells.***
  *(Text from case report: for option A)*

**Explanations to options: Text from case report**

- ***'In contrast to myeloproliferative disorders where Eosinophils are part of the Neoplastic clone, eosinophilia in patients with ALL is believed to be a reactive process.'*** – Case report
- ***'A normal karyotype has been observed in 45% of patients of ALL/Eo and t (5:14) rearrangement has been documented in same of them.'*** – *Case report*
- 'The child was treated with MCP-841 protocol of NC2 (prednisolone, L-asparginine, vincristine and daunarubicin) and was in remission after 4 weeks of chemotherapy. ***However, the peripheral blood eosinophils and the pulmonary symptoms normalized 6 weeks after attaining remission.*** – *Case report.*

## Acute Myeloblastic Leukemia (AML)

**295. Answer is A (M2):** *Atlas of Hematologic Neoplasms (Springer) 2009/115; Harrison's 18th/Chapter 109*

***Acute Myeloblastic Leukemia (AML) with maturation (FAB-M2) is the most common subtype of AML, accounting for approximately 25–45% of AML cases.***

**296. Answer is A (Monosomy) :** Harrison 18th/p 905, 910 *Wintrobe's 12th/1859, 1861*

***Monosomy is consistently associated with an unfavorable or poor prognosis.***

**Monosomy is associated with a poor prognosis**

*Monosomy especially those involving chromosome 7 (monosomy 7) and chromosome 5 (monosomy 5) are consistently associated with poor prognosis in both adults and children with AML*

**Deletion of X or Y chromosome is associated with a favorable / intermediate prognosis**

*'Monosomy of the X chromosome in a female patient (loss of the Y chromosome) is the most common whole chromosome loss identified in pediatric patients with AML. This numeric abnormality is usually associated with t(8; 21) translocation and AML M2 which carry a good prognosis' - 'Childhood Leukemias' by Puri 2nd/253*

*'Loss of Y and X chromosomes are most frequently observed in patients with t(8; 21) which carries a favourable prognosis' - 'Blood: Principles and Practice of Hematology' 2nd/108*

**Nucleophosphin mutation is associated with a favorable prognosis**

| *Factor* | *Favourable* | *Unfavourable* |
|---|---|---|
| Nucleophosphin mutation | Present | Absent |

**t (8; 21) translocation is associated with a favorable prognosis**

| *Factor* | *Favourable* | *Unfavourable* |
|---|---|---|
| Cytogenetics | t(15;17),<br>***t(8;21),***<br>inv(16) | -7, del(7q),<br>-5, del(5q),<br>3q21 and 3q26 abnormalities, complex karyotypes |

**Prognostic Feature in Acute Myeloid Leukemia:**

| **Factor** | **Favourable** | **Unfavourable** |
|---|---|---|
| **Clinical** | | |
| *Age* | *<45 yr* | *<2yr, >60yr* |
| *ECOG performance status* | *0-1* | *>1* |
| *Leukemia* | *De novo* | *Antecedent hematologic disorder, myelodysplasia, myeloproliferative disorder* |
| *Infection* | *Absent* | *Present* |
| *Prior chemotherapy* | *No* | *Yes* |
| *Leukocytosis* | *<25,000/mm3* | *>100,000/mm2* |
| *Serum LDH* | *Normal* | *Elevated* |
| *Extramedullary disease* | *Absent* | *Present* |
| *CNS disease* | *Absent* | *Present* |
| *Cytoreduction* | *Rapid* | *Delayed* |
| **Morphology** | | |
| *Auer rods* | *Present* | *Absent* |
| *Eosinophils* | *Present* | *Absent* |
| *Megaloblastic erythroids* | *Absent* | *Present* |
| *Dysplastic megakaryocytes* | *Absent* | *Present* |
| *FAB type* | *M2, M3, M4* | *M0, M6, M7* |
| **Surface/enzyme markers** | | |
| *Myeloid* | *CD34-, CD14-, CD13-* | *CD34+* |

| | | |
|---|---|---|
| *HLA-DR* | *Negative* | *Positive* |
| *TdT* | *Absent* | *Present* |
| *Lymphoid* | *Cd2+* | *CD7+, CD56+*<br>*Biphenotypic (2 or more lymphoid markers)* |
| *MDR-1* | *Absent* | *Present* |
| **Cytogenetics** | | |
| *Cytogenetics* | *t(15;17), t(8;21), inv(16)* | *-7, del(7q), -5, del(5q), 3q21 and 3q26 abnormalities, complex karyotypes* |
| **Molecular markers** | | |
| *Fms-related tyrosine kinase-3 mutation* | *Absent* | *Present* |
| *Ecotropic viral integration site 1 expression* | *Absent* | *Present* |
| *Mixed-lineage leukemia partial tandem duplication* | *Absent* | *Present* |
| *Nucleophosphin mutation* | *Present* | *Absent* |
| *CCAAT/enhancer-binding protein-α mutation* | *Present* | *Absent* |
| *Brain and acute leukemia cytoplasmic gene expression* | *Absent* | *Present* |
| *Vascular endothelial growth factor expression* | *Absent* | *Present* |

**297. Answer is B (M3):** *Surgical Pathology of Head & Neck (volume 2) by Barnes (CRC Press) 2001/1343*

*Auer Rods are most frequently seen in AML – M3 (FAB).*

**Auer Rods and Acute Myeloid Leukemia (AML)**

Auer Rods are crystalline, refractile, azurophilic rod shaped structures made from alignment of granules that are typically seen in AML (may be seen in refractory anemia with excess blasts in transformation)

- *Auer Rods are most frequently seen in AML-M3 (95-100%) and AML-M2 (70%)*[Q]
- *Auer Rods are absent by definition in AML-M0*[Q]
- *Auer Rods are usually not seen in AML-M5a and AML-7*[Q]
- *Auer Rods may be seen in other subtypes of AML in < 30-50% of cases*

**Auer Rods in AML**

| Most Frequently seen in (Typical Findings in) | Absent in (By Definition) | May be seen in other subtypes (30-50%) |
|---|---|---|
| • *AML M3 (95-100%)*<br>• *AML M2 (70%)* | *AML – M0*<br>Usually not seen in AML 5a and AML 7 | *AML M1*<br>*AML M4*<br>*AML M6* |

**298. Answer is A (AML – M0):** *Surgical pathology of Head & Neck (2001)/1343*

*Auer Rods by definition are absent in AML-M0.*

*'Auer Rods by definition are absent in AML-M0 and usually not seen in AML-M5a and AML-M7. Auer rods are most often present in AML-M3 (95-100%) and AML-M2 (70%) and are seen in 30-50% of the other subtypes'*

*- Surgical Pathology of Head & Neck*

**299. Answer is D (Presence of t 8 : 21):** *Harrisons 16th/634; Harrison 17th/677,678,680; CMDT 2008/448; CMDT 2009/453*

*Patients with t (8, 21), t (15 : 17) or inv (16) have extremely good prognosis*
*The single most important prognosis factor is attainment of complete remission.* [Q]

The Likelihood of entering complete remission and hence the prognosis is determined by the following factors :

**Age of Diagnosis** :

- ***> 60 years has a poor prognosis***
- Chronic intercurrent ***disease***, acute medical problems with increasing age are associated with poor prognosis.

**Chromosome findings :**

| Prognosis | Chromosome Findings |
|---|---|
| Good | t (8 : 21), t (15 : 17), inv (16) |
| Moderate | No cytogenetic abnormality |
| Poor | Monosomy 5 and 7, Complex karyotype, Inv(3) |

**Presenting Leucocyte count** :

- A high presenting Leucocyte count is an independent prognostic factor
- Duration of CR is inversely related to presenting Leucocyte count

  Among patients with ***hyperleucocytosis (>100,000/μg)*** early central nervous system bleeding and pulmonary leukostasis and Late relapse contribute to poor outcome.

**Prolonged symptomatic interval with cytopenias - Antecedent hematological disorder**

- Poor prognosis is seen in patients with anemia, Leukopenia, thrombocytopenia for duration of more than 1 month before diagnosis.
- Poor prognosis is seen in patients with **secondary Leukemias** developing after treatment with cytotoxic agents / irradiation.

**Other Prognostic features :**

- FAB classification
- Characteristics of Leukaemic cells : e.g. *Auer Rods* $^{Q}$ *- poor prognosis*
- Expression of *MDRI Gene* $^{Q}$ *- poor prognosis*

**300. Answer is D (Immediately start induction chemotherapy):** *Harrison's Manual of Oncology 1st/207; 'Treatment of Acute Leukemia' br Pei 1st/259; 'Hematology-Oncology Therapy' 1st/220*

*Immediate treatment of Hyperleukocytosis is leukocytoreduction which is generally achieved by Leukopharesis or administration of Hydroxyurea.*
*Induction chemotherapy is initiated early in treatment after attempts at leukocytoreduction but not immediately.*

***Immediate induction chemotherapy is the single best answer of exclusion.***

*Immediate Administration of induction chemotherapy to a patient with hyperleukocytosis carries a high risk of Acute tumor lysis syndrome and hence induction chemotherapy is often not initiated immediately but generally follows attempts at cytoreduction.*

*IV hydration, Allopurinol and alkalinization of urine are measures to reduce the metabolic complications of tumor lysis syndrome and are indicated as preventive measures in patients with Leukostasis and hyperleukocytosis.*

**Hyperleukocytosis and Leukostasis** (Independent poor prognostic factor in acute leukemia)

- Hyperleucocytosis is a condition in which patients with acute leukemia present with an extraordinary high leukocyte count usually greater than 100,000.

  The high number of circulating blasts increase the blood viscocity and predispose to the development of Leukostasis.
- Leukostasis refers to sludging of leukemia blasts in the microcirculation leading to obstruction of small vessels especially in the cerebral and pulmonary circulations.
- Once identified leukostasis requires immediate and effective treatment to lower the blast count rapidly.

Treatment of Hyperleukocytosis

| Immediate Cytoreduction /Leukoreduction | Initiation of Induction Chemotherapy | Supportive / Preventive of Complications |
|---|---|---|
| Leukostasis requires immediate and effective treatment to lower the blast count.<br>This may be achieved by<br>Leukopharesis<br>Hydroxyurea | • Initiation of chemotherapy is also critical for the treatment of Leukostasis since blasts removed from circulation by cytoreduction are rapidly replaced by blasts from bone marrow.<br>However<br>*Induction chemotherapy is not initiated 'immediately' but generally follows attempts at cytoreduction.*<br>*Early chemotherapy is advised but not necessarily 'immediate' chemotherapy.* | • IV hydration<br>• Allopurinol<br>• Alkalinization of urine } To prevent complication of tumor lysis syndrome<br>*Initiation of induction chemotherapy carries the risk of Acute Tumor lysis syndrome and hence these supportive measures are instituted.* |

**301. Answer is D (Monosomy 7):** *Harrisons 16th /634; CMDT 2006/509; CMDT 2009/453; Hematology by Hoffman 4th/1128*

*Monosomy 7 is associated with a very poor prognosis. Patients with t (8, 21), t (15; 17) and inv (16) have a good prognosis.*

**Cytogenic studies are most powerful prognostic factors (CMDT)**

| Good Prognosis | Moderately favourable prognosis | Poor prognosis |
|---|---|---|
| • t(8:21)<br>• Inv (16) (p13, q22)<br>• t(15; 17) | • No cytogenic abnormality | • Complex karyotype<br>• Monosomy 7 (-7)<br>• Monosomy 5<br>• Del 5q<br>• 3q rearrangement<br>• Inv. (3)<br>• FLT3 internal tandem duplication |

**302. Answer is D (Monosomy 7) :** *Harrison 18th/p 910; CMDT 2008/448; CMDT 2009/453; Repeat*

*Patient with a complex karyotype, inv (3), or -7 (monosomy) have a poor prognosis.* **- *Harrison***

**303. Answer is C (CD15 / 34 both seen in same cell) :** Harrison 18th/p 905, 906, 912 *Harrison 16th /632-634; Harrison 17th/ 678, 682; Robbins 7th /693; CMDT 2006/508-509; Ghai 6th / 567; CMDT 2008/446*

*CD15 and CD34 are not associated with Acute Promyelocytic leukemia.*

| **Acute promyelocytic Leukaemia (PML : FAB M3)** |
|---|
| • This is a type of Acute Myeloid Leukaemia (AML) and has been classified as the M3 category according to the FAB morphological classification.[Q]<br>• It constitutes 5 – 10% of all AML (Robbin's / Ghai) |
| **Pathological characteristic of PML** |
| • It is ***characterized by the chromosomal translocation t(15;17)***[Q] *– CMDT*<br>• ***t(15;17) translocation*** produces a fusion gene ( PML-RAR )involving the Retinoic Acid Receptor gene and Promyelocytic Leukemia (PML) gene.<br>This PML – RaR fusion protein tends to suppress gene transcription and blocks differentiation of cells.<br>***This block can be overcome with pharmacological doses of retinoic acid*** (Harrrison).<br>• *Most cells are hypergranular*[Q] promyelocytes often with many Auer rods per cell. |
| **Presentation characteristic / Specific features of PML** |
| • Patients of PML are younger (median age 35 – 40 years) – Robbin's<br>• ***Incidence of Disseminated Intravascular Coagulation (DIVC) is*** high in patient with PML. *–Robbin's*<br>*DIC may occur with any subgroup of AML but is especially common in acute PML (M3)*–Ghai |

| Treatment specific to PML subject |
|---|
| All-Trans Retinoic Acid (ATRA/Tretinoin) |
| • ***The treatment of patient with PML has been dramatically improved by the use of All – Trans – Retinoic acid.*** *This agent is an analog of vitamin A that leads to terminal differentiation of occult promyelocytic leukemia cells. - CMDT* |
| • *Remission in PML is induced by All – Trans-Retinoic acid as a single agent –Ghai* |
| Arsenic Trioxide |
| Arsenic Trioxide produces meaningful response in upto 85% of patients refractory to tretinoin |

**304. Answer is C (Promyelocytic Leukemia):** Harrison 18th/p 907 *Hematology by Hoffman 4th/1087; Harrisons 17th/679: Appendix A2*

*Acute promyelocytic Leukemia (APL) characteristically presents with Thrombocytopenia, prolonged PT, Prolonged PTT, hypofibrinogenemia and increased levels of fibrin degradation product as it is associated with a high incidence of DIC.*

***The patient in question is presenting with an elevated PT, elevated PTT, Thrombocytopenia (platelets 35,000) and decreased fibrinogen levels (Normal fibrinogen levels = 233-496 mg/dl) All these features are characteristic of DIC which is a common mode of presentation in APL. APL is the single best answer of choice.***

**Characteristic presentation of APL**

- Patients are typically younger than other subtypes of AML
- Patients typically present with bleeding tendencies and/or DIC (as DIC is common in APL)

| Features of DIC |
|---|
| *Thrombocytopenia* |
| *Prolonged prothrombin time (PT)* |
| *Prolonged Partial Thromboplastin Time (PTT)* |
| *Increased Fibrin Degradation products (N=0-1 ug/ml)* |
| *Decreased Fibrinogen levels (N=233-496 mg/dl)* |

**305. Answer is A (Acute promyelocytic leukemia):** *Harrison 18th/p912, 913; CMDT 2008/448; CMDT 2009/453*

***Arsenic trioxide has been approved for the treatment of relapsed disease in Acute promyelocytic leukemia (PML).*** – CMDT

**Treatment of Acute Promyelocytic Leukemia (M3-FAB-AML)**

Acute promyelocytic leukemia is treated differently from all other subtypes of AML and has become the most curable type of AML of adults.

Treatment Agents

| Chemotherapy | All-Trans Retinoic Acid (ATRA) (Vitamin A/Tretinoin) | Arsenic Trioxide |
|---|---|---|
| Standard chemotherapy especially Anthracycline antibiotics | • ATRA has revolutionized the treatment of PML<br>• ATRA is capable of inducing Complete Remission as a Single agent in PML<br>• ATRA is part of induction therapy in PML (along with an anthracycline antibiotic for chemotherapy) | • ***Arsenic trioxide has been approved for the treatment of relapsed disease in APL***<br>• *Arsenic trioxide can provide meaningful response in upto 85% of patients refractory to tretinoin* |

## Biphenotypic Leukemia

**306. Answer is A (Biphenotypic leukemia):** *Principles and Practice of Pediatric Oncology 5th/172 Wintrobe's 11th/2108 Blood by Hadden Lux and Stossel 1st/492*

***Biphenotypic leukemias are leukemias that express features of more than one lineage. The patient in question has a rare leukemia that expresses both, myeloid antigens (CD 33 and CD 13) and Lymphoid antigens of B cell lineage (CD 10 and CD 19) and hence can be described as a Biphenotypic leukemia.***

**Biphenotypic Leukemias**

- Biphenotypic Leukemias are rare acute leukemias that express both myeloid and lymphoid associated antigens to a degree that no single lineage can be assigned.

- Scoring systems have been proposed to more precisely defines biphenotypic leukemias and to distinguish these cases from 'ALL with myeloid antigen expression' or 'AML with lymphoid antigen expression'

Scoring System for Biphenotypic Acute Leukemia

| Points | B Lineage | T Lineage | Myeloid Lineage |
|---|---|---|---|
| 2 | CD79a<br>Cyt IgM<br>Cyt CD22 | CD3 (m/cyt)<br>Anti-TCR α/β<br>Anti-TCR γ/δ | Anti-MPO (monoclonal)<br>MPO cytochemistry |
| 1 | CD19<br>CD10<br>CD20 | CD2<br>CD5<br>CD8<br>CD10 | CD117<br>CD13<br>CD33<br>CD65s<br>Anti-MPO (polyclonal) |
| 0.5 | TdT<br>CD24 | TdT<br>CD7<br>CD1a | CD14<br>CD15<br>CD64 |

M, membrane; cyt, cytoplasm; MPO, myeloperoxidase

A diagnosis of biphenotypic acute leukemia requires a score of more than 2 points for the myeloid and one of the lymphoid lineages.

*The patient in question scores two points for myeloid lineage and two points for lymphoid B cell lineage and hence can be classified as a Biphenotypic Leukemia*

## Plasma Cell Disorders / Multiple Myeloma

**307. Answer is D (Dystrophic classification):** Harrison 18th/p 938, 939; *16th/ 657, 658, 659; Harrison 17th/ 702, 703*

***Multiple myeloma is associated with hypercalcemia and as a result metastatic calcification may occur. Dystrophic calcification is not a feature.***

**MULTIPLE MYELOMA**

Malignant proliferation of plasma cells in the bone marrow results in production of large number of complete and incomplete immunoglobulins

Suppression of normal hematopoietic cells in marrow
- Anemia (normocytic normochromic)

Proliferation of plasma cells in bone and activation of osteoclasts activating factor
- *Lytic lesions* ♀
  - Bone pain
  - Pathological fractures
  - Cord compression
- *Hypercalcemia*
  - Metastatic calcification (not dystrophic ♀)
  - Osteoporosis

**Increased number of abnormal immunoglobulins**

- Precipitation in kidney (kidney damage)
  - Bence Jones Light chain Proteinuria ♀
  - ***Renal failure*** ♀ *(Amyloidosis may occur* ♀*)*
- Ineffective defence against infections ♀
  - ***Recurrent Infections*** ♀
- Interference with clotting factors
  Amyloid damage of endothelium
  - ***Bleeding tendency*** ♀ *(May be seen due to failure of antibody coated platelets to function properly or due to the interaction of M component with clotting factors I,II,V,VII or VIII)*
- ***Hyperviscosity*** ♀
  - *Neurological* ♀ *Manifestations*
    - Vertigo, Tinnitus
    - *Headache* ♀
    - *Visual disturbance* ♀
- ***Cryoglobulinemia*** *(Type-1)*
  - *Monoclonal Cryoglobulins are commonly seen in Multiple Myeloma*
  - *Raymond's phenomenon and impaired circulation may result if the M Component forms cryoglobulin*

**308. Answer is D (Dystrophic calcification):** *Text below*

***Multiple myeloma may be associated with metastatic calcification (not dystrophic calcification).***

*Multiple myeloma is associated with hypercalcemia and as a result metastatic calcification may occur. Dystrophic calcification is not a feature.*

**309. Answer is D (Hyperviscosity syndrome):** *Harrison 18th/938, 939; 'The Cleveland Clinical Internal Medicine Case Reviews' (Lippincott Williams) 2003/page 141 (MCQ); Oxford Desk Reference: Oncology (2011)/509*

***Hyperviscosity syndrome is an uncommon /infrequent complication/presentation of Multiple myeloma.***

**Hyperviscosity syndrome is an infrequent/uncommon complication/presentation of multiple myeloma**

*The Monoclonal 'M' component in Multiple Myeloma usually consists of monoclonal IgG or monoclonal IgA.* Hyperviscosity syndrome from monoclonal IgG/IgA in multiple myeloma is an infrequent/uncommon event, though when present it is potentially destructive.

| |
|---|
| *Hyperviscosity syndrome is commonly seen with monoclonal IgM as in Waldenstrom's Macroglobulinemia* |

*'Although potentially destructive hyperviscosity is a relatively uncommon complication of multiple myeloma'*

*– The Cleveland Clinic Internal Medicine Case Review*

*'Patients with multiple myeloma develop hyperviscosity infrequently' – Oxford Desk Reference*

| |
|---|
| *In Multiple Myeloma, Hyperviscosity has been described in 3-4% of IgG Myeloma and 5-10% of IgA Myeloma.* |

**Bone pain (skeletal destruction), Anemia and Susceptibility to bacterial infections are frequent/common features of Multiple Myeloma**

Bone Pain

*'Bone Painis the most common symptoms in myeloma affecting nearly 70% of patients' – Harrison 18th/938*

Susceptibility to Bacterial Infection

*'The most common clinical problem (after skeletal destruction) in patients with multiple myeloma is susceptibility to bacterial infections'*

*'>75% of patients will have a serious infection at some time in their course and recurrent infections are the presenting feature in approximately 25% of patients.' – Harrison 18th/938*

Anemia

*'Normocytic Normochromic anemia is present in approximately 80% of myeloma patients' – Harrison 18th/939*

| Clinical Feature of M. Myeloma | Approximate frequency |
|---|---|
| Bone pain/skeletal Destruction | ~ 70% (***Most common presenting feature***) |
| Recurrent bacterial Infection | ~ > 25% (*Presenting feature in > 25%*) |
| Renal failure | ~ > 25% (*Renal Failure occurs in ~ 25% of MM patients*) |
| Hypercalcemia | ~ 25% (*About 25% of patients develop Hypercalcemia at some stage of disease. It is the most common cause of Renal failure in MM patient*) |
| Anemia (Normocytic Normochromic) | ~ 80% (*Normocytic Normochromic anemia occurs in approx. 80% of patients.* It is usually not a presenting feature.) |

**310. Answer is A (Lytic bone lesions ):** *'Blood' by Handin 2nd/890; Hematology in Clinical Practice 4th/306*

*Multiple Myeloma is now widely defined in accordance with the Durie and Salmon diagnostic criteria .The diagnostic criteria are divided into major and minor criteria.* ***Lytic bone lesions constitute minor criteria in accordance with the classification system. All other options are part of the major criteria that define multiple myeloma.***

**Diagnosis and Staging of Multiple Myeloma (The Durie and Salmon myeloma diagnostic criteria)**

- The Durie and Salmon myeloma diagnostic criteria are used widely in the United States and have been validated by large multicenter trials.
- The diagnostic criteria are divided into major and minor.

*The diagnosis of Multiple Myeloma requires a minimum of one major and one minor criterion or three minor criteria as defined in the table below*

- Once the diagnostic criteria for multiple myeloma are met, Durie-Salmon clinical staging can be used to determine the stage of disease.

**Criteria for Diagnosis of Multiple Myeloma**

| **Major criteria** |
|---|
| 1. *Plasmacytomas on tissue biopsy* |
| 2. *Bone marrow plasmacytosis (> 30% plasma cells)* |
| 3. *Monoclonal immunoglobulin spike (M spike) on serum electrophoresis:*<br>*IgG > 3.5 g/dl or*<br>*IgA > 2.0 g/dl*<br>*κ or λ light-chain excretion > 1.0 g/d on 24-h urine protein electrophoresis.* |
| **Minor criteria** |
| a. *Bone marrow plasmacytosis (10-30% plasma cells)* |
| b. *Monoclonal immunoglobulin spike present but of lesser magnitude than in 3* |
| c. *Lytic bone lesions* |
| d. *Supressed Uninvolved Immunoglobulin*<br>*Normal IgM <50mg/dl or*<br>*Normal IgA <100 mg/dl or*<br>*Normal IgG <600 mg/dl.* |
| *Any of the following sets of criteria will confirm the diagnosis.* |
| *Any two major criteria*<br>*Major criterion 1 plus minor criterion b, c or d*<br>*Major criterion 3 plus minor criterion a or c*<br>*Minor criteria a, b and c or a, b and d* |

**311. Answer is C (Plasmacytoma on Tissue Biopsy):** *'Blood' by Handin 2nd/890; Hematology in Clinical Practice 4th/306*

***Plasmacytoma on tissue biopsy is a major criterion for diagnosis of Multiple Myeloma and not a minor criterion.***

**312. Answer is C (Plasmacytoma on tissue biopsy):** *Refer Previous Question; William's Hematology 7th/1507*

***Plasmacytoma or tissue biopsy is a major criterion for diagnosis of multiple myeloma (and not a minor criterion)***

**313. Answer is C (Plasmocytosis > 2%):** *Harrison 18th / 940; 15th/ 730; Harrison 16th/ 659; Harrison 17th/ 703, 704*

*Diagnosis of Multiple Myeloma requires plasmacytosis of > 10%.*

| **The classic triad of myeloma is:** |
|---|
| a) *Marrow plasmacytosis > 10%* |
| b) *Lytic bone lesions* |
| c) *Serum or urine 'M' component* |

**314. Answer is D (IgD):** *Immunology & Serology in Laboratory Medicine (Elsevier Health Sciences, 2013)5TH/ 369*

*The M component in Multiple Myeloma can be made up of the immunoglobulins IgG, IgM, IgD, IgA, and IgE; light chains alone; or heavy chains alone.* ***IgG Myeloma is the most common form of Multiple Myeloma while IgD (2%) and IgE (Rare) are the least common.***

**Distribution of immunoglobulin types in patients with multiple myeloma**

| Type of protein | Percentage (%) |
|---|---|
| IgG | 52 |
| IgA | 22 |
| IgM | 12 |
| IgD | 2 |
| IgE | Rare |

**315. Answer is A (IgG):** *Immunology & Serology in Laboratory Medicine (Elsevier Health Sciences, 2013)5TH/ 369*

*The M component in Multiple Myeloma can be made up of the immunoglobulins IgG, IgM, IgD, IgA, and IgE; light chains alone; or heavy chains alone.* ***IgG Myeloma is the most common form of Multiple Myeloma while Ig D (2%) and IgE (Rare) are the least common.***

**316. Answer is A (t(11;14)):** *Harrison 18th/ 937; The Washington Manual of Surgical Pathology(Lippincott Williams & Wilkins, 2008)/ 566; The Principles of Clinical Cytogenetics(Springer, 2013)/ 426*

***The most common translocation seen in patients with Multiple Myeloma is t(11;14).***

*'The most common translocation seen in patients with Multiple Myeloma is t(11;14)(q13;q32) involving the BCL1 locus on chromosome 11q13 and the immunoglobulin heavy (IgH) chain locus on chromosome 14q13 which leads to overexpression of Cyclin D1'- The Washington Manual of Surgical Pathology*

*'The two most common translocation seen in patients with Multiple Myeloma are t(11;14)and t(4;14). Both these translocations occur with almost similar frequencies, however the incidence of translocation t(11;14) appears to be marginally higher. Patients with t(4;14) fall within a poor prognosis subgroup, while those with t(11;14) have a standard risk' - The Principles of Clinical Cytogenetics*

| **The two most common translocation seen in patients with Multiple Myeloma** |
|---|
| • t(11;14)(q13;q32) : Associated with standard prognosis<br>• t(4;14) (p16;q32) : Associated with aggressive behaviour and poor prognosis |

***Q The most common translocation in multiple myeloma associated with a poor prognosis is translocation t(4;14)***

**317. Answer is B (t(4;14)):** *Harrison 18th/ 937; The Washington Manual of Surgical Pathology(Lippincott Williams & Wilkins, 2008)/ 566 ; The Principles of Clinical Cytogenetics(Springer, 2013)/ 426*

***The most common translocation associated with poor prognosis in patients with Multiple Myeloma is t(4;14).***

*'The two most common translocation seen in patients with Multiple Myeloma are t(11;14)and t(4;14). Both these translocations occur with almost similar frequencies, however the incidence of translocation t(11;14) appears to be marginally higher. Patients with t(4;14) fall within a poor prognosis subgroup, while those with t(11;14) have a standard risk' - The Principles of Clinical Cytogenetics*

| **The two most common translocation seen in patients with Multiple Myeloma:** |
|---|
| The most common translocation associated with poor prognosis in patients with Multiple Myeloma is t(4;14)<br>The most common translocation associated with standard prognosis in patients with Multiple Myeloma is t(11;14) |

**318. Answer is B (t (8-14) translocation):** *Harrison 18th/p 938 Harrison 15th/ 729, 16th/ 657; Harrison 17th/ 702, 703*

- A variety of chromosomal alterations have been found in patients with Multiple myeloma. The most common translocation is t (11; 14) (q 13; q32). 13q14 deletions and 17p13 deletions and 11q abnormalities predominate. *Translocation t(8-14) has not been mentioned.*
- Complete Immunoglobulin chain comprises of both heavy chains and light chains. But ***in Multiple myeloma there is excess production of light chains*** Q over heavy chains.
  ***These light chains are eliminated in urine as Bence Jones protein.*** Q
  ***Protein cast in urine are thus made up of light chains only*** Q (not complete immunoglobulin chains).
- *'Bone lesions in multiple myeloma are lytic in nature* and are rarely associated with osteoblastic new bone formation.' – *Harrison.*
  Bone lesions in MM are caused by the proliferation of tumor cells and activation of osteoclasts that destroy the bone.
  *'Bone pain is the most common symptom in MM affecting 70% of patients* Q *' - Harrison*

**319. Answer is B (Translocation t (8;14)):** *Harrison 18th/ 937; The Principles of Clinical Cytogenetics(Springer, 2013)/ 426*

***Multiple myeloma is not associated with translocation t(8;14).***

*The two most common translocation seen in patients with Multiple Myeloma are t(11;14) and t(4;14). Both these translocations occur with almost similar frequencies, however the incidence of translocation t(11;14) appears to be marginally higher. Patients with t(4;14) fall within a poor prognosis subgroup, while those with t(11;14) have a standard risk.*

**320. Answer is D (Protein casts in urine are made up of complete Ig chains):** *Harrison 16th/657, 658, 659; 17th/ 703, 704*

***Protein casts in urine are made up of light chains only and not complete I g chains.***

- Complete lg chain comprises of both heavy chain & light chain.
  *In Multiple myeloma there is* ***excess production of light chains*** *over heavy chains. These light chains are eliminated in urine as* ***Bence Jones Protein.***
- Multiple myeloma represents a clonal proliferation of plasma cells derived from a single clone.
  - Thus there is an elevation of only one chain of immunoglobulins which forms the 'M' component with a reciprocal depression of other classes of immuno globulins.
  - The M component is most commonly formed by IgG.
  - Serum protein electrophoresis thus shows a monoclonal spike corresponding the this M component.
- It is rare under age of 40 and the median age at diagnosis in 68 years.
- Amyloid glomerulopathy may occur – Harrisons.

**321. Answer is A (Vertebral column):** *Robbins 6th/ 664; 7th/679*

***The commonest site of involvement in multiple myeloma is vertebral column.***

**Although any bone may be involved, the following order of involvement is most often seen.**

| ***Vertebral column (66%) > Ribs (44%) > Skull(41%) > pelvis (28%) > femur (24%) > clavicle(10%) > scapula(10%)*** |
|---|

**322. Answer is D (Renal failure):** Harrison 18th/p 938, 939 *Harrison 17th/703, 702, 704*

***Renal failure occurs in nearly 25% of Myeloma patients and some renal pathology is noted in over half.*** *–Harrison 17th/703*

**Multiple Myeloma is associated with Lytic bone lesion and Bone Resorption**

The bone lesions of Myeloma are caused by activation of osteoclasts that destroy bone and suppression of osteoblasts that form bone.

***Bone lesions are thus lytic in nature and not sclerotic.***

***There is a net resorption of bone and not bone deposition.***

**Multiple Myeloma is associated with Hypercalcemia and not Hypocalcemia**

*Hypercalcemia is caused by substantial mobilization of calcium from bone due to associated bony lysis.*

**323. Answer is C (Bone scan) :** Harrison 18th/p 940, 941 *Harrison 16th / 658, 659; Harrison 17th/ 703, 704, 705; Other references*

***Bone scans are least useful for diagnosis of Multiple Myeloma. Cytokines secreted by myeloma cells suppress osteoblastic activity therefore typically no increased uptake is observed.***

***In multiple myeloma the osteoblastic response to bone destruction is negligible. The bone scan therefore is often normal or may show areas of decreased uptake (photopenia).It has been found to be less useful in diagnosis than plain radiography.***

**Diagnosis of Multiple Myeloma** (*Harrison 16th & Others)*

| Serum Markers | Urine examination | Skeletal survey | Bone marrow aspire biopsy |
|---|---|---|---|
| ▪ **Full blood count / Differential count**<br>-Anemia ♀<br>▪ **Biochemical profile :**<br>–↑ serum calcium<br>–↑ urea / creatinine<br>–↑ uric acid<br>▪ **Albumin / Globulin Ratio** : Reversed<br>▪ ***ESR : Elevated***<br>▪ **Quantitative Ig levels (IgG, IgA, IgM)**<br>-Elevated Myeloma protein<br>-Supressed non myelomatous Ig<br>▪ **Serum Protein electrophoresis**<br>-Characteristic M spike<br>▪ **Serum Alkaline Phosphatase**: *Normal*<br>▪ **β2 microglobulin** :<br>*Most important predictor of outcome.*<br>▪ **C – Reactive protein & IL6 levels** :<br>*-CRP is useful as a prognostic marker*<br>-CRP is surrogate marker of IL6 activity (IL6 is often referred to as plasma cell growth factor) | **24 hour urine specimen** to quantitate protein excretion (> 1g protein /24 hour is a major ciriteria for diagnosis<br><br>**Urine protein electrophoresis** to identity Bence Jones protein | **X rays**<br>Perform complete skeletal series including skull chest, pelvis, spine & long bones<br>-Lytic bones<br>-Diffuse osteopenia<br><br>**MRI scan**<br>MRI is useful in symptomatic patients with normal radiographs<br>Sensitive means to document cord or root compression | • Calculate % of plasma cells in marrow **aspirate** (Normal < 3%)<br><br>• Look for a sheets or clusters of plasma cells in biopsy specimens.<br><br>• Cytogenetic analysis of bone marrow may give prognostic information (Abnormalities of chromosome 13 eg. C13q deletion indicates poor prognosis.) |

**Note :**

- *Serum M component is most commonly IgG ♀ (IgG (53%), IgA (25%), IgD (1%)*
- *Bence Jones proteins are light chain protein only ♀.*

**324. Answer is A (Protein Electrophoresis):** Harrison 18th/p 938, 940, 941 *Harrison's 17th/703, 704, 705*

*Presence of symptoms of hyperviscocity syndrome (Headache), recurrent infections (ineffective defense against infections) and multiple punched out lytic lesions in the skull suggest a diagnosis of Multiple myeloma*

***Protein electrophoresis will help demonstrate a characteristic 'M spike' and help in establishing the diagnosis of multiple myeloma.***

*Serum Calcium is likely to be elevated while serum alkaline phosphatase levels are likely to be normal. Although both serum calcium and serum alkaline phosphatase levels may be done to support a diagnosis of Multiple Myeloma, demonstration of the charachteristic 'M spike' on protein electrophoresis is the single preferred investigation.*

| Classic Triad of Multiple Myeloma | Relevant investigations |
|---|---|
| • Marrow plasmacytosis > 10% | (*Bone Marrow examination*: Not provided in options) |
| • Lytic bone lesions | (*X-Ray skull*: Already performed in patient) |
| • Serum/urine M component | (***Protein Electrophoresis***: *Suggested next investigation*) |

**325. Answer is B (Increased in alkaline phosphatase):** Harrison 18th/p 939, 940 *Harrison 16th/ 659; Harrison 17th/ 704*

***Serum alkaline phosphatase is usually normal even with extensive bone involvement because of the absence of osteoblastic activity – Harrison 16th/ 659***

**Laboratory parameters in multiple myeloma :**

- Anaemia: Normocytic normochromic
- ESR♀ : markedly increased
- Hypogammaglobulinemia♀
- Monoclonal spike on Serum protein electrophoresis - Monoclonal Gammopathy (M Band)

- Bone marrow replacement of normal marrow elements by plasma cells.
- Bence Jones Proteinuria: Light chain proteinuria (inclomplete IgG)
- Uric Acid level : Elevated due to increased cell turnover
- Serum calcium : Elevated
- Alkaline phosphatase : Normal
- Neutropenia & Thrombocytopenia rare

**326. Answer is C (Increased alkaline phosphatase):** Harrison 18th/p 938, 939, 940 *Harrison 15th/ 730, Harrison 16th/ 659; Harrison 17th/ 703, 704*

***Serum Alkaline phosphatase is usually normal even with extensive bone involvement because of absence of osteoblastic activity*** *– Harrisons 16th/ 659*

- Bone pain is the most common symptom in myeloma Q
- Bone lesions are lytic in nature and are rarely associated with osteoblastic new bone formation. Therefore

- Radioisotope bone scanning is less useful in diagnosis than plain radiography Q
- No hot spot is seen on bone scan Q
- Alkaline phosphatase (marker of osteoblastic activity) is not raised.

**327. Answer is B (Multiple myeloma):** *Harrison 18th/p 940, 2529; Harrison 17th/704, 1925*

**Serum alkaline phosphatase** ***is usually normal in multiple myeloma.***

**Alkaline phosphatase** consists of many distinct isoenzymes and can be elevated in a number of conditions affecting Liver, Bone, placenta & small intestine.

**Causes of elevated alkaline phosphatase**

| **Physiological:** | **Liver derived Alkaline phosphatase:** |
|---|---|
| • Patients over age > 60 y<br>• Individuals with blood group O & B after a fatty meal<br>• Adolescents and children undergoing rapid bone growth.<br>• Late in normal pregnancy. | • Elevation of less than three times normal can be seen in any liver disease<br>• Elevation of rather than four times normal suggests<br>- Cholestatic liver disease<br>- Infiltrative liver disease eg. cancer. |
| **Bone derived Alkaline phosphatase:** | **Miscellaneous conditions:**<br>(Isolated elevation of serum alkaline phosphatase) |
| • Elevation suggests increased bone turn over / increased osteoblastic activity such as<br>- Paget's disease<br>- Rickets & osteomalacia | 1. Hodgkin's disease<br>2. Diabetes<br>3. Hyperthyroidism<br>4. Congestive heart failure<br>5. Inflammatory bowel disease. |

**328. Answer is D (Elevated alkaline phosphatase):** *Refer previous question .*

***Serum alkaline phosphatase is characteristically normal even with extensive bone involvement because of absence of osteoblastic activity*** *– Harrison*

*Anemia, Hypercalcemia and Hyperviscocity are recognized features of multiple myeloma.*

**329. Answer is C (Multiple myeloma):** *Harrison 18th/p 940; 17th/ 704; Hematology manual KGMC*

***ESR is elevated in multiple myeloma*** *– Harrisons 16th/ 659*

| **Conditions with decreased ESR that need to be remembered** | |
|---|---|
| 1. *Polycythemia* Q | 3. *Sickle cell anemia* Q |
| 2. *CHF* Q | 4. *Afibrinogenimea* |
| **Conditions with increased ESR that need to be remembered :** | |
| 1. *Pregnancy* Q | 5. *Leucocytosis* Q |
| 2. *Menstruation* Q | 6. *New born* Q |
| 3. *Multiple myeloma* Q | 7. *DLE* Q |
| 4. *Anemia other than sickle cell* Q | |

**330. Answer is A (Anion Gap Raised):** *Refer text below; High Yield 'Acid Base Balance' 2nd/10*

***Multiple Myeloma is associaitd with decreased Anion Gap.***

| Causes of Decreased Anion Gap |
|---|
| • Hypoalbuminemia<br>• Multiple Myeloma and other paraproteinemic states like Waldenstorm's macroglobulinemia<br>• Lithium intoxication / Bromide intoxication |

*Decreased Anion Gap is rare / uncommon and occurs due to accumulation of positively charged unmeasured cations which lower the anion gap*
*This is important as it may mask a significant anion gap acidosis.*

**331. Answer is C (Polyclomal gammapathy):** Harrison 18th/p 937, 940 *Harrison 17th/701*

***Mulitple Myeloma is characterized by monoclonal gammapathy and not polyclonal gammapathy.***

*Multiple myeloma represents a malignant proliferation of plasma cells derived from a single clone (monoclonal)* – *Harrison 17th/701*

*Bone marrow cells are monoclonal – Harrison 17th/703*

**332. Answer is D (Plasmacytosis < 10%):** *Harrison 17th/703; Internal Medicine 5th/565; Clinical Hematology and Oncology 1st (2003)/202; Clinical Laboratory Medicine 6th/347*

***Multiple myeloma is characteristically associated with Plasmacytosis >10%.***

**Multiple myeloma may be associated with both Hypogammaglobulinemia and Hypergammaglobulinemia.**

**Electrophoresis Pattern in Multiple Myeloma**

| Monoclonal Hypergammaglobulinemia (M spike) | Hypogammaglobulinemia |
|---|---|
| This is the characteristic electrophoresis pattern in Myeloma | • About 10-20% of multiple myeloma patients present with Hypogammaglobulinemia on electrophoresis.<br>• This configuration is suggestive of light chain variant of multiple myeloma in which Bence Jones proteins are excreted into urine without a serum myeloma protein being evident with routine electrophoresis techniques. |

*'Multiple Myeloma results in hypergammaglobulinemia of a specific class of immunoglobulins. Hypogammaglobulinemia also justifies a search for myeloma especially for the possibility of light chain disease.'*
– *Guide to Diagnostic Testing 1st (2002)/259*

**Multiple Myeloma may be with Bence Jones Proteins, Amyloidosis & Renal failure**

**333. Answer is A (multiple mycloma):** *Robbins 7th/680*

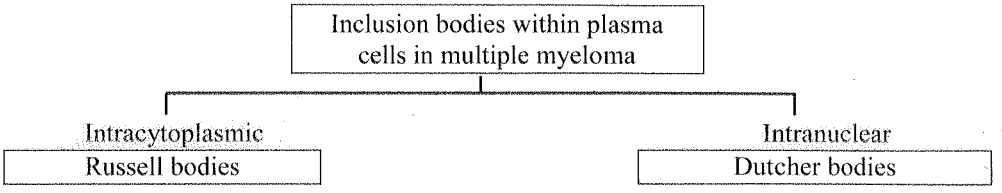
***Russell bodies are intracytoplasmic inclusion bodies seen in within plasma cells in multiple mycloma***

Characteristic Pathological features of multiple myeloma
(Not specific for multiple myeloma and may also be seen in benign disorders)

| Cell types/shapes | Inclusion Bodies |
|---|---|
| • Plasma blasts<br>• Bizzare multinucleated cells<br>• Flame cells (cells with cherry red cytoplasm)<br>• Mott cells (cells with multiple blue grape like cytoplasmic droplets) | • Russell bodies (intracyloplasmic)<br>• Dutcher bodies (nuclear)<br>• Inclusions of fibrils, crystalline rods and globules |

**334. Answer is D (Plasma cells):** *Robbins 7th/680*

*Russel bodies are intracytoplasmic inclusion bodies seen within plasma cells in patients with multiple myeloma.*




**335. Answer is C (Multiple Myeloma):** *Teaching Atlas of Musculoskeletal Imaging (Thieme, 2011)/261*

*The appearance of skull in multiple myeloma with multiple osteolytic "punched-out" lesions has been typically referred to as the Raindrop skull.*

*The pattern of destruction seen in the skull affected by myeloma has been described as a rain drop", demonstrating multiple lytic lesions of different sizes, but usually intermediate to large. This should not be mistaken for the "pepper pot" or "salt and pepper" pattern seen in hyperparathyroidism, where the lucent lesions tend to be innumerable uniform small foci on a back-ground of normally mineralized skull.*

**336. Answer is B (Hypocalcemia):** Harrison 18th/p 940 *Harrison 17th/704; Clinical Malignant Hematology 1st (2007)/916; 'manual of Clinical Oncology' 6th/482, 483*

*Hypercalcemia is associated with a poor prognosis in Multiple Myeloma and not hypocalcemia.*
*Azotemia (↑ creatinine), ↑ LDH, Chromosome 13q deletion and High M component production are all established poor prognostic factors.*

**Poor prognostic factors in Multiple Myeloma**

| Stage Related Factors | Independent factors |
|---|---|
| Stage III disease : High Tumor Burder<br>• Hb < 8.5 g/dl<br>• Hypercalcemia (Ca > 12 mg/dl)<br>• Advanced Lytic bine lesions<br>• High M component production<br>IgG > 7g/dl<br>IgA > 5g/dl<br>Urine light chains > 12g/24 hrs<br>Subclassification based on serum creatinine levels<br>• Serum creatinine > 2 mg/dl | • β2 microglobulin (single most important factor)<br>• ↓ Serum albumin<br>• ↑ LDH<br>• ↑ labeling index (%age of cells undergoing mitosis)<br>• ↑ CRP or IL6<br>• ↑Hepatocyte growth factor, TGF (β) or syndecan – 1<br>• Plasmoblastic morphology<br>• Genetic Abnormalities<br>- Hyperploidy<br>- Chromosome 13 deletion (and chromosome 17 p deletion)<br>- t(4; 14), t(14; 16), t(11; 4) translocation<br>- RAS & P53 mutations. |

**337. Answer is C ($\beta_2$ microglobulin):** *Harrison 18th/p 941 Harrison 15th/ 731; Harrison 16th/ 659; Harrison 17th/ 704*

*Serum $\beta_2$ microglobulin is the single most powerful predictor of survival and can substitute for staging-H-16th*

| $\beta_2$ microglobulin level | Median survival |
|---|---|
| < 0.04 g/L | Median survival of 43 months |
| >0.04 g/L | Median survival of only 12 months. |

**338. Answer is C (Multiple myeloma):** Harrison 18th/p 938, 940 *Harrison 16th/658; Harrison 17th/ 703, 704*

*Backache and Recurrent infections in the backdrop of normal alkaline phosphatase levels and a reversed albumin globulin ratio (A : G ratio) is highly suggestive of the diagnosis of multiple myeloma.*

**Interpretation of information provided in the question**

| Clinical information | | Laboratory parameters | | | |
|---|---|---|---|---|---|
| **Infomation** | **Interpretation** | **Parameter** | **Normal** | **Patients** | **Interpretation** |
| • Backache | • Bony pains | • Haemoglobin | 12 - 16gm | 7.3 | ***Anemia*** |
| • Weakness of legs & urinary retention | • Cord compression | • Serum $Ca^{++}$ | 9.0 - 10.5mg/dl | 12.6 | ***Hypercalcemia*** |
| • Chest infection (recurrent) | • Ineffective defence against infection | • Alkaline phosphatase | 30-120 U/l | 100 | ***Normal*** |
| | | • Albumin | 3.5 - 5.5 gm/dl | 3.0 | Normal |
| | | • Globulin | 2.0 - 3.5 gm/dl | 7.1 | ***Elevated*** |
| | | • Urea | 20 - 40 mg/dl | 178 | Elevated |

***Both clinical findings and laboratory data suggest the diagnosis of Multiple Myeloma***

- Serum Alkaline Phosphatase is usually normal even with extensive bone involvement.– *Harrison*
- Serum Albumin is normal or low, Total protein is normal or raised.– *Kumar 5th/501*



**339. Answer is B (Multiple myeloma):** *Harrison 18th/940, 941 Harrison 15th/ 728, Harrison 16th/ 659; Harrison 17th/ 704*

***This is a 65 year old patient presenting with low back pain along with-a reversed A: G ratio. This indicates an excess of globulin fraction or a possible gammopathy. These findings along with an elevated ESR and Renal involvement (indicated by increased creatinine levels) suggest a diagnosis of Multiple Myeloma.***

**340. Answer is B (Hydroxyurea):** *NCCH Clinical Practice Guidelines in oncology; Harrison's 18th/941, 942*

***Hydroxyurea is not recommended for the management of multiple myeloma***

**Chemotherapeutic Agents Recommended in the management of multiple myeloma**

- *Bortezomib*
- *Cyclophosphamide*
- *Doxorubicin*
- *Vincristine*
- *Lenalidomide*
- *Thalidomide*
- *Melphelan*
- *Dexamethasone / Prednisolone*
- *Interferon (Maintenance)*

The most commonly used chemotherapy agents in non-transplant and transplant candidates and in relapsed or refractory myeloma, based on the *2007 National Comprehensive Cancer Network (NCCN) guidelines*

| Primary Induction therapy for transplant candidates | Primary Induction Therapy for non-transplant Candidates |
|---|---|
| • *Bortezomib/dexamethasone (category 1)*<br>• *Bortezomib/cyclophosphamide/dexamethasone*<br>• *Bonezomib/doxorubicin/dexamethasone (category 1)*<br>• *Bortezomib/enalidomide[e]/dexamethasone (category 2B)*<br>• *Bortezomib/thalidomide/dexamethasone (category 1)*<br>• *Dexamethasone (category 2B)*<br>• *Lenalidomide[e]/dexamelhasone (category 1)*<br>• *Liposomal doxorubicin/vincristine/dexamethasone (DVD) (category 2B)*<br>• *Thalidomide/dexamethasone (category 2B)* | • *Bortezomib/dexamethasone*<br>• *Dexamethasone (category 2B)*<br>• *Lenalidomide/low-dose dexamethasone (category 1)*<br>• *Liposomal doxorubicin/vincristine/dexamethasone (DVD) (category 2B)*<br>• *Melphalan/prednisone (MP)*<br>• *Melphalan/prednisone/bortezomib (MPB) (category 1)*<br>• *Melphalan/prednisone/thalidomide (MPT) (category 1)*<br>• *Melphalan/prednisone/lenalidomide (MPL)*<br>• *Thalidomide/dexamethasone (category 2B)*<br>• *Vincristine/doxorubicin/dexamethasone (VAD) (cateoory 2B)* |
| **Maintenance Therapy** | **Salvage** |
| • *Interferon (category 2B)*<br>• *Lenalidomide[f]*<br>• *Steroids (category 2B)* | • *Repeat primary induction therapy (if relapse at > 6 mo)*<br>• *Bendamustine (category 2B)*<br>• *Bortezomib[g] (category 1)* |

| | |
|---|---|
| • *Thalidomide (category 1) ± prednisone (category 2B)* | • *Bortezomib/dexamethasone*<br>• *Borlezomib/lenalidomide/dexamethasone (category 2B)*<br>• *Bortezomib/liposomal doxorubicin[g] (category 1)*<br>• *Cyclophosphamide-VAD*<br>• *Cyclophosphamide/bortezomib/dexamethasone[h]*<br>• *Cyclophosphamide/lenalidomide/dexamethasone[h]*<br>• *Dexamethasone*<br>• *Dexamethasone/cyclophosphamide/etoposide/cisplatin (DCEP)*<br>• *Dexamethasone/thalidomide/cisplatin/doxorubicin/ cyclophosphamide/etoposide (DT-PACE)*<br>• *High-dose cyclophosphamide*<br>• *Lenalidomide/dexamethasone (category 1)*<br>• *Lenalidomide*<br>• *Thalidomide*<br>• *Thalidomide/dexamethasone* |

*[a]Selected, but not inclusive of all regimens →Thalidomide/dexamethasone*
*[b]Treatments are listed alphabatically and do not imply preference.*
*[c]Recommend herpes zoster prophylaxis for patients treated with bortezomib*
*[d]Prophylactic anticoagulation recommended for patients receiving thalidomide-based therapy or lenalidomide with dexmethasone.*
*[f]Lenalidomide as maintenance has been evaluated in three independent randomized clinical trials. Results from each of these trials show improvements in TTP. The panel felt that this warranted inclusion: however, this recommendation remains Category 2A since these results have not undergone full peer review and safety/efficacy data are still preliminary.*
*[g]Bortezomib/liposomal doxorubicin is prefered to bortezumib single agent*
*[h]These are representative regimens combining standard agents with novel agents.*

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical tirals is especially encouraged.

**341. Answer is C (Hydroxyurea):** *Harrison's 17th/705.*

*Hydroxyurea is not used in the management of Multiple Myeloma.*

## Multiple Myeloma Variance and Other Plasma Cell Disorders

**342. Answer is A (Monoclonal gammopathy):** Harrison 18th/p 940 *Hariosn 17th/704*

*Smoldering myeloma is a variant of multiple myeloma and is associated with a monoclonal gammopathy*

**Smoldering Myeloma**

- Smoldering Myeloma is an asymptomatic variant of multiple myeloma (Monoclonal gammopathy)
- These patients have a higher levels of M-component and marrow plasmacytosis than patients with **MGUS** (Monoclonal Gammopathy of Unknown Significance), and fulfill the minimal criteria for diagnosis of plasma cell myeloma, but are asymptomatic and have no lytic bone lesions or other clinical features of Myeloma.

Diagnostic Criteria for Smoldering Myeloma (Asymptomatic Myeloma)

*M protein is serum > 30g/L (>3g/dl)*
*Bone marrow clonal plasma cell (Plasmacytosis) ≥ 10%*
*No myeloma related organ or tissue impairment*
- *No lytic bone lesions*
- *No myeloma related symptoms*
  - *No renal insufficiency*
  - *No Anemia*
  - *No Hypercalcemia*

Comparisonof MGUS, Indolent myeloma and Smoldering myeloma:

| | MGUS | SMM | IMM | Multiple Myeloma |
|---|---|---|---|---|
| **Plasma cell (BM)** | <10% | 10-30% | >30% | >30% |
| **M-component** | IgG<3.5, IgA<2 | IgG>3.5, IgA>2 | IgG 3.5-7, IgA 2-5 | IgG >3.5/dl; IgA >2g/dl |
| **Lytic bone lesion** | None | None | ≤3 | Present |
| **Symptoms/Infection**<br>- *Anemia*<br>- *Renal insufficiency*<br>- *Hypercalcemia* | None | None | None | Present |

**343. Answer is C (Monoclonal gammopathy of unknown significance):** *Harrison 18th/p 940; Harrison 17th/ 704, 706*

*'Patients with monoclonal gammopathy of uncertain significance have < 10% bone marrow plasma cells, and < 3g / dl of M component', - Harrison 15th / 730*

*Presence of 8% bone marrow plasma cells and 1.5 gm/dl of M component in the form of IgG in this patient thus lead us to the above diagnosis.*

**Plasma cell dyscrasia : Monoclonal gammopathies : Paraproteinemias : dysproteinemias**

These are monoclonal neoplasms characterized by expansion of a single clone of immunoglobulin secreting cells (plasma cells) and result in increase in serum levels of a single homogenous 'immunoglobulin' or – its fragments (light chains or heavy chains).

*The most important differential diagnosis in patients with multiple myeloma involves their distinction from individuals with MGUS or Benign monoclonal gammopathy:*

| Parameters | Multiple myeloma | Monoclonal gammopathy of undetermined significance |
|---|---|---|
| 1. Age $^{Q}$ | > 50 years | > 50 years |
| 2. Incidence $^{Q}$ | Less common | More common |
| 3. Plasma cells $^{Q}$ (%age) | > 10% | < 10% |
| 4. M component $^{Q}$ (concentration : g/dl) | > 3g/dl | < 3g/dl |
| 5. Benze Jones $^{Q}$ proteins | Present | No urinary Bence Jones proteins |
| 6. Clinical features $^{Q}$ | Lytic bones lesions<br>Hypercalcemia<br>Renal failure<br>Anemia | No Lytic bony lesions$^{Q}$<br>No hypercalcemia$^{Q}$<br>No renal failure$^{Q}$<br>No anemia$^{Q}$ |
| 7. Labelling index $^{Q}$ (Thymidine) | > 1% | < 1% |
| 8. Plasma cell<br>- acid phosphatase<br>- glucoronidase | <br>High<br>High | <br>Low<br>Low |
| 9. Treatment | Required | No therapy required |

**Woldenstorm's macroglobulinemia:** is also a monoclonal gammopathy and is characterized by neoplasm of lymphoplasma cytoid cells that secrete IgM

*M component is only IgM and not IgG.*

| This is characterized clinically by |
|---|
| - Lymphadenopathy<br>- Hepatosplenomegaly<br>- Hyperviscosity syndrome |

**Indolent multiple myeloma (IMM):**

Lies in the spectrum between MM and MGUS

| Unlike MGUS, patients with IMM have - | Unlike MM patients with IMM |
|---|---|
| > 10% plasma cells<br>> 3g / dl of M protein | - are Asymptomatic<br>- Patients have mild non progressive anemia but no bone lesions, hypercalcemia or renal failure<br>- Progress to overt MM in < 1 years |

**344. Answer is B (Multiple myeloma):** *Harrison 18th/p 938, 940, 941; Harrison 17th/ 703, 704; 705*

***This is a** 60 year **patient presenting with** generalized bone pain and lytic lesion in skull **with blood parameters indicating a** markedly raised ESR, Hypercalcemia, Hyperglobulinemia and raised serum creatinine. **All these** suggest a diagnosis of multiple myeloma.*

| | Patient | Normal | Interpretation & inference |
|---|---|---|---|
| Age | 60 years | - | 60 years |
| ESR | 100 | < 15 (male) | Markedly increased |
| Serum globulin | 7 | 2.5 to 3.5 | Increased |
| Serum creatinine | 3.5 | < 1.5 mg/dl | Increased: Renal failure |
| Serum calcium | 11.0 | 9 mg/dl | Increased hypercalcemia |

**Distinguishing features between W. Macroglobulinemia from multiple myeloma**

- **Does not cause lytic bone lesions**
- **Does not cause hypercalcemia* serum calcium is usually not elevated***
- **Serum 'M' component is IgM**
  - IgM being large in size undergoes Less renal excretion
  - Renal disease is not common $^{Q}$
    Serum creatinine is usually not elevated.
- Hepatomegaly, splenomegaly and lymphadenopathy are common unlike in multiple myeloma where they are uncommon.
- Symptoms due to hyperviscocity are more prominent as compared to those in multiple myeloma
  - Epistaxis visual disturbance and neurological symptoms are more common.
  - Rouleaux formation and positive Coombs test are more common.

**345. Answer is B (A diagnosis of plasma cell leukemia .....):** *Wintrobe's haematology 11th/ 2620, 2593*

*'Plasma cell leukaemia' by definition is characterized by more than 20% plasma cells in the peripheral blood. The patient in question has 14% plasma blasts in peripheral blood and thus does not classify as a plasma cell leukaemia.*

**Distinguishing features in various types of plasma cell disorders:**

**Plasma cell leukaemia (Rare form of plasma cell disorder)** *Wintrobe's 11th/ 2620*

- ***More than 20% plasma cells*** in the peripheral blood
- Absolute plasma cell count of more than $2 \times 10^9$/L

**IgD Myeloma** *(Wintrobe's 11th/ 2592)*

- Accounts for approximately 2% of all cases of myeloma
- Presence of Monoclonal IgD in the serum usually indicates IgD myeloma
- ***Present with a small bond or no evident M-spike on serum protein electrophoresis.***
- Higher incidence of renal insufficiency, Amyloidosis and proteinuria than IgG / IgA myeloma.
- Higher incidence of Extramedullary involvement and inferior survival rates.

**Monoclonal gammopathy of undetermined significance**

- Serum monoclonal protein < 3 g/dl
- No anemia, renal failure, or hypercalcemia
- Bone lesions absent on radiographic bone survey
- Bone marrow < 10% plasma cells.

**Smoldering multiple myeloma**

- Serum monoclonal protein (≥ 3 g/dl) or ***≥ 10% marrow plasma cells*** or aggregates on biopsy, or both
- No anemia, renal failure, or hypercalcemia attributable to myeloma

**Multiple myeloma**

- ***Monoclonal protein presents in serum or urine***
- ≥ 10% marrow plasma cells on biopsy of histologic evidence of plasmacytoma
- Plus one or more more of the following
  - Anemia
  - Lytic lesions or osteoporosis and ≥30% plasma cells in marrow
  - Bone marrow plasma cell labeling index >1%
  - Renal insufficiency
  - Hypercalcemia

*Criteria for diagnosis of Monoclonal Gammopathy of Undetermined Significance, Smoldering Multiple Myeloma and Multiple Myeloma, According to Kyle and Greipp-Wintrobes.*

**346. Answer is A (Multiple Myeloma):** *Harrison 18th/938,939*

*Plasmacytoma on tissue biopsy and Bone marrow plasmacytosis with >30 percent plasma cells are two major criteria for the diagnosis of Multiple Myeloma. Presence of any two major criteria is believed to confirm the diagnosis of multiple myeloma.*

*The clinical complex of bone pain and **renal failure** together with diagnostic observation of skeletal destruction, **hypercalcemia,** monoclonal 'M' spike, tissue plasmacytoma and bone marrow plasmacytosis >30 percent confirms a diagnosis of Multiple Myeloma*

***MGUS** is typically associated with < 10 % plasma cells on bone marrow biopsy.*

***Solitary Plasmacytoma and Smoldering myeloma** are by definition/criteria not associated with any myeloma related symptoms (Anemia, Hypercalcemia, and Renal Failure)*

**347. Answer is B (Plasmacytoma):** *Multiple Myeloma and Related Plasma Cell Disorders (Springer, 2004)/112*

***Presence of a solitary lytic lesion of the bone with monoclonal plasma cells suggests a diagnosis of Solitary Plasmacytoma of Bone**. A small M spike may be identified in some patients but Bone Marrow biopsy taken some distance away from the primary site is typically not involved typically showing < 10 percent plasma cells*

**Solitary Bone Plasmacytoma**

The diagnosis of SBP requires histologic evidence of a monoclonal plasma cell infiltrate in a single bone lesion, absence of other bone lesion on skeletal survey, and lack of marrow plasmacytosis elsewhere. Furthermore, there should be no evidence of anemia, hypercalcemia, or renal dysfunction that could be attributed to the plasma cell proliferative disorder

| Diagnostic criteria for Solitary Plasmacytoma of bone and Extramedullary Plasmacytoma |
|---|
| • Solitary Osseous lesion or Extramedullary lesion due to clonal plasma cell proliferation<br>• Normal marrow with no evidence of clonal plasma cells or aneuploidy by flow-cytometry.<br>• Normal skeletal survey with proximal humeri and femora and a<br>  • Normal magnetic resonance image of the axial skeleton (for Solitary Plasmacytoma of Bone); or a<br>  • Normal regional computed tomographic scan (for Extramedullary Plasmacytoma).<br>• Absent or low serum or urinary concentration of monoclonal protein.<br>• No anemia, hypercalcemia, or renal insufficiency attributable to myeloma. |

*A small M spike may be identified in some patients but Bone Marrow biopsy taken some distance away from the primary site is not involved typically showing < 10 percent plasma cells.*

**348. Answer is B (Seligmann Disease):** *Harrison's 18th/944*

*Alpha Heavy Chain Disease (Seligmann's Disease) is the most common of the heavy chain diseases.*

**Heavy Chain Diseases**

Heavy chain diseases are Plasma Cell Dyscrasias Characterized by elevated levels of a specific heavy chain of immunoglobulins in blood and urine

| *Heavy Chain* | *Feature* |
|---|---|
| *Gamma chain* | ***Also known as Franklin's disease***<br>***Seen in elderly resemble lymphoma.*** |
| *Alpha chain* | ***Also known as Saligmann's disease***<br>***This is the most common heavy chain disease*** |
| *mμ chain* | ***Rarest form of Heavy Chain disease***<br>***May produce monoclonal light chains, typically of kappa type*** |

**349. Answer is A (Gamma heavy chain disease):** *Harrison 18th/p 943, 944 Harrison 17th/ 707; Read text below*

*Franklin's disease is a gamma heavy chain disease.*

**350. Answer is A (Mu chain disease):** *Hematology in clinical practice. 4th/25; Harrison's 18th/Chapter 111*

*Heavy Chain Disease most commonly associated with kappa light chains in urine is Mu Chain Disease.*

Heavy chain diseases (HCDs) are rare B-cell lymphoproliferative neoplasias characterized by the production of a monoclonal component consisting of a truncated monoclonal Ig heavy chain without the associated light chain. The production of light chains is a rare event in Heavy chain diseases. In mu heavy chain disease however, the neoplastic cells may produce monoclonal light chains, usually of kappa type, that fail to assemble with the truncated heavy chain and are excreted in the urine as Bence Jones protein.

*The only features that may distinguish patients with mu heavy chain disease from patients with chronic lymphocytic leukemia are the presence of vacuoles in the malignant lymphocytes and the excretion of kappa light chains in the urine.*

## Bleeding / Coagulation Disorder

### General

**351. Answer is B (IX and X):** *Ganong 23rd/535, Chaudhry physiology 6th/73*

*Vitamin K dependent coagulation factors include coagulation factor II, VII, IX and X.*

**Vitamin K dependent Coagulation Factors / Proteins**

- Six proteins involved in clotting require conversion of a number of glutamic acid residues to γ - carboxyglutamic acid residues before being released into circulation
- This process of γ (gamma) carboxylation occurs in the liver and requires vitamin k and hence these proteins are called vitamin – K dependent
- These include coagulation factors II, VII, IX and X as well as protein C and protein S.

Vitamin K dependent proteins involved in clotting

- ***Coagulation Factor II$^{Q}$ (Prothrombin)***
- ***Coagulation Factor VII$^{Q}$ (Proconvertin)***
- ***Coagulation Factor IX$^{Q}$ (Christmas factor)***
- ***Coagulation factor X (Stuart Prover Factor)***
- *Protein C$^{Q}$*
- *Protein S$^{Q}$*

**352. Answer is A(II):** *Refer text below; CMDT 2008/466; CMDT 2009/481*

*Vitamin K dependent factors include factors II, VII IX and X*

Vitamin K dependent factors: Factor II, VII, IX, X

**353. Answer is B (P.T.):** *CMDT 2008/466; CMDT 2009/481; Read text below*

*Although PT and PTT both will be affected PT is the single best answer as explained below.*

**Vit K dependent factors :** Factor II, VII, IX & X $^{Q}$

Therefore both intrinsic & extrinsic mechanisms of the coagulation cascade are affected. (Refer previous questions) PT & PTT both will be prolonged.

***However**, factor VII has short t½ & so PT is the first to be prolonged (even in mild vit. K deficiency)*

*Later, factors II, IX & X will also fall, causing PTT to be prolonged. PT is thus the better choice out of PT and PTT.*

**354. Answer is A (Prolonged prothrombin time):** *Ghai 6th/31; CMDT 2008/466,467; CMDT 2009/481*

*Hemorrhagic disease of new born results from a deficiency of vitamin K.*

*Prothrombin time is the single best laboratory test to detect vitamin K deficiency as vitamin k deficiency may present with isolated prolongation of PT*

Laboratory features of vitamin k deficiency (CMDT-2008)

- Both PT and PTT are prolonged but prolongation of PT is a more sensitive test to detect vitamin K deficiency than PTT
  - *The PT is prolonged to a greater extent than PTT*
  - *With mild vitamin K deficiency only the PT is defective*
- Fibrinogen level, Thrombin time and platlet count are not affected – CMDT

**355. Answer is B (Vitamin C deficiency):** *Harrison 18th/599;15th/ 464; 16th/406, 407, 409; 17th/ 445*

*Bleeding manifestations with normal prothrombin time and clotting time almost confirms the diagnosis of vitamin C deficiency.*

**Bleeding manifestations due to vitamin deficiency**

| VITAMIN C | VITAMIN K |
|---|---|
| • Vitamin C is required for synthesis of collagen which forms part of capillary walls.<br>• Vitamin C deficiency leads to increased capillary wall fragility and hence increased manifestations of haemorrhagic areas such as–<br>- *over lower extremities*[Q]<br>- *around hair follicles*[Q]<br>- *nail beds*[Q] | • Vitamin K dependent factors include Factor II, VII, IX, X<br>• In vitamin K deficiency bleeding occurs due to lack of coagulation factors |
| • Patient presents with<br>- increased bleeding time [Q]<br>- normal PTT, PT, TT [Q]<br>- normal clotting time[Q] | • Patient presents with<br>- increased clotting time[Q]<br>- increased PTT, PT, TT[Q]<br>- normal bleeding time[Q] |

**356. Answer is A (Prolonged bleeding time (BT) :** *Robbins 7th / 653; KDT 5th / 172;*

*Bleeding time is indicative of function of platelets. Aspirin ingestion results in defective platelet function and hence the deranged parameter will be Bleeding time. PT, APTT and Clotting time (CT) are parameters of coagulation defects, and will be normal in isolated disorders of platelet function.*

***'Ingestion of Aspirin and other Nonsteroidal Antiinflammatory drugs, significantly prolongs the bleeding time'.***
*– Robbin 7th / 653*

*'Aspirin even in small doses irreversibly inhibits T xA2 synthesis by platelets.* ***Thus it interferes with platelet aggregation and bleeding time is prolonged to nearly twice the normal value'****-KDT 5th / 172*

**Note:**

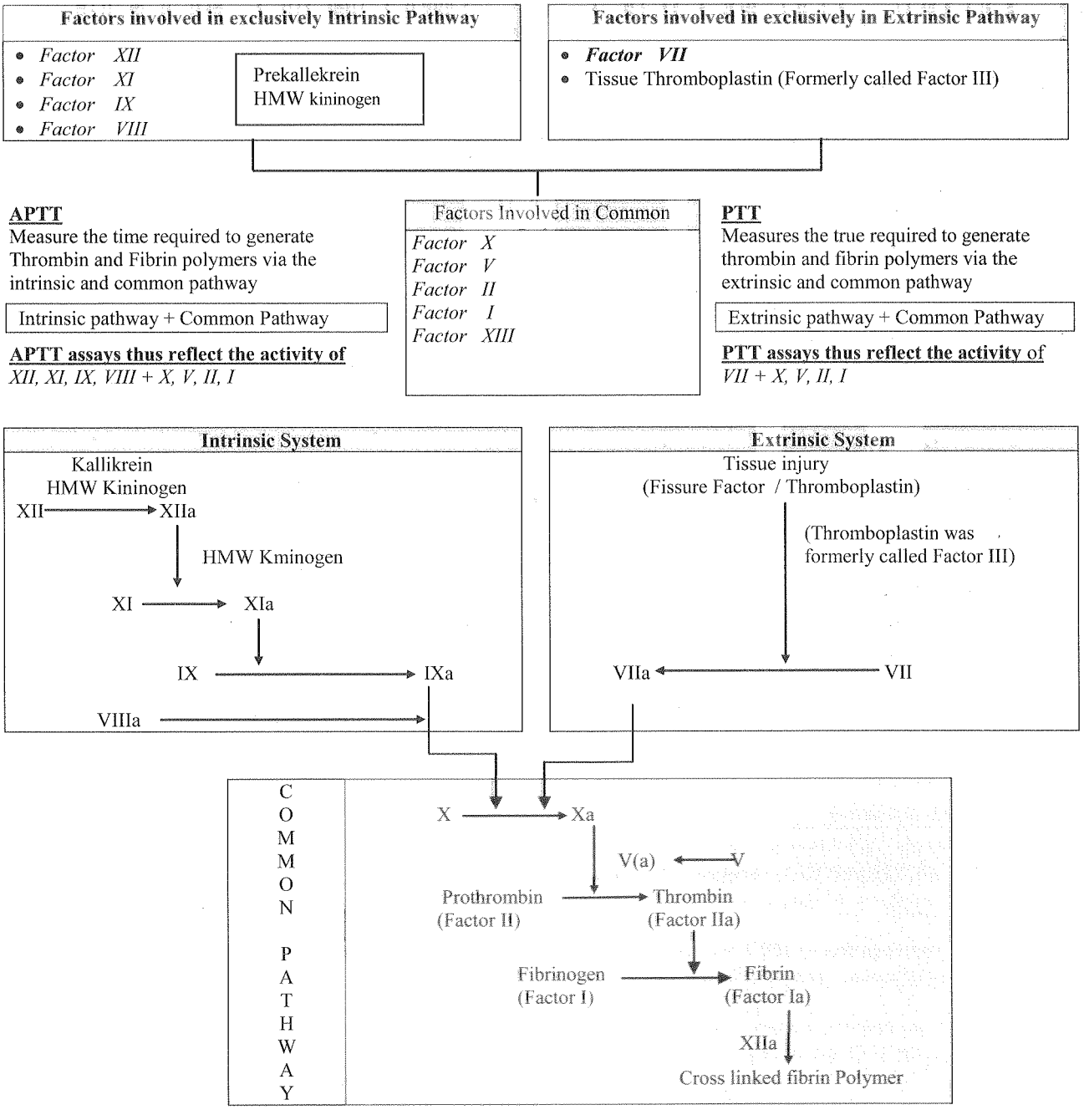
- *Aspirin* ***irreversibly*** [Q] ***inhibits COX –1 and COX*** *– 2. (Harrison)*
  *COX inhibition leads to prevention of TXA2 synthesis and impairment of platelet secretion and aggregation*
- *The effect of aspirin on platelet function* ***occur within 1 hour and lasts for the duration of the affected platelet's life span ie. 1 week.*** [Q] *– Harrison*

**357. Answer is A and B (Platelet adhesion Assays and BT):** *Refer text below*

*Platelet function may be assessed by 'Bleeding time' and Platelet Adhesion Assays.*

**358. Answer is D (Factor VII) :** *Refer text below; Ganong 22nd/ 542; Robbins 7th / 128; Clinical Hematology 4th / 355*

***Factor VII is involved in the extrinsic pathway of coagulation and plays no role in the intrinsic pathway.***




**359. Answer is A (Factor XIII)** : *Ganong 22nd/ 543; Harrisons 17th /364;Refer previous question*

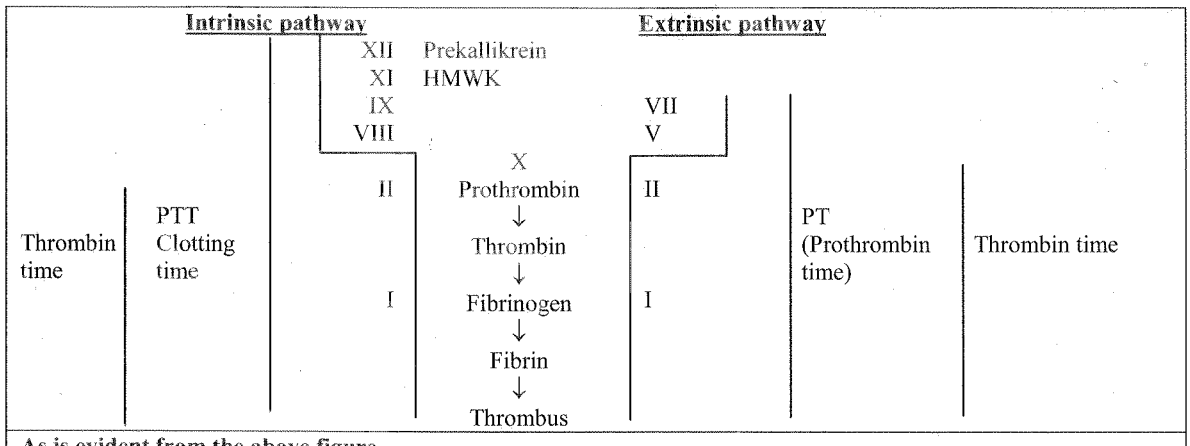
***Factor XIII is also known as fibrin stabilizing factor. Activated factor XIII (XIIIa) covalently cross links and stabilizes the fibrin clot*** – *Harrison*

*The fibrin is initially a loose mesh of interlacing strands. It is converted into a dense, tight aggregate (Stabilization) by the formation of covalent cross linkages. This reaction is* ***catalyzed by activated factor XIII*** *and requires calcium.*

*-Harrison*

**360. Answer is B (Stuart factor X):** *Refer text below: Refer previous question*

*The extrinsic and Intrinsic pathways in coagulation converge at the stuart factor X.*




**As is evident from the above figure**

***PTT is prolonged with deficiency of factors*** : *XII, XI, IX, VIII, II, I and Thrombin*

***PT is prolonged with deficiency of factors*** : *VII, V, II, I and Thrombin*



**361. Answer is B (Factor VII deficiency):** *CMDT 2008/467; Refer previous question*

***Factor VII deficiency may present with isolated prolongation of prothrombin time.***

*Deficiency of factor VIII, IX and XII may present with isolated prolongation of Partial Thromboplastin Time (APTT) and not isolated prolongation of prothrombin time (PT)*

| Cause of Isolated prolongation of PT (CMDT) |
|---|
| ***Vitamin K deficiency*** |
| *Warfarin therapy* |
| *Liver disease* |
| *Factor VII deficiency* |

**362. Answer is C (Lupus Anticoagulant):** *Practical Hemostasis and Thrombosis; Harrison's 17th/369; Wintrobe's 12th/1447-1453; 'Clinical Anesthesia' 6th (Lippincott William's)/187, 'Complications in Surgery' by Doherty (2006)/187*

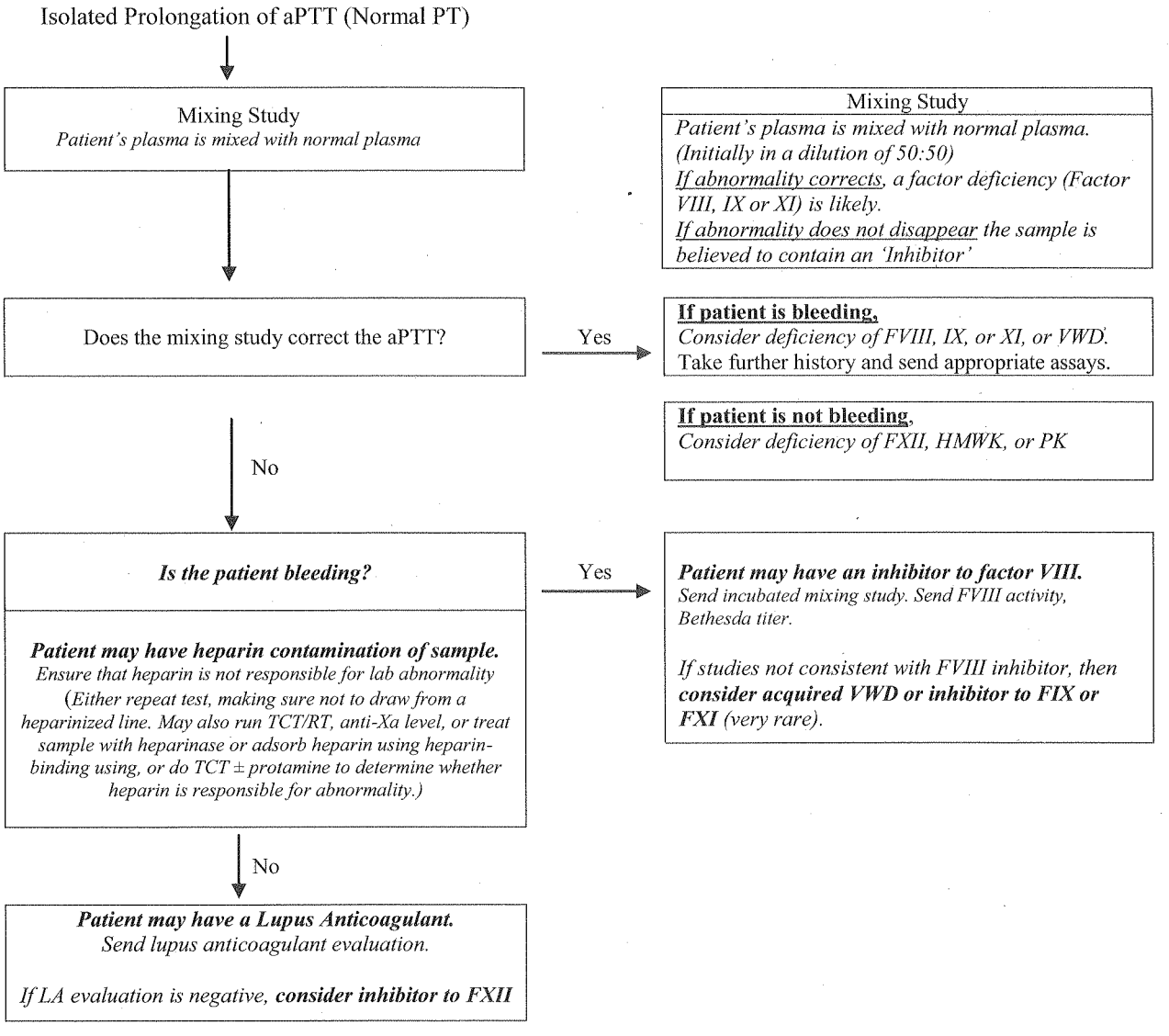
***Isolated prolongation of aPTT with no clinical history of bleeding suggests the presence of Lupus anticoagulant or deficiency of contact factors (Factor XII, Prekallikrein or HMWK)***

*'If there is no bleeding history, but the APTT alone is prolonged, the most likely cause of prolonged aPTT is a lupus anticoagulant'* - *'Complications in Surgery' by Doherty (2006)/187*

**Approach to a patient with isolated prolongation of activated Partial Thromboplastin time (aPTT)**

- The Partial Thromboplastin Time (aPTT) is a performance indicator measuring the efficacy of both the '*intrinsic system' and the 'common' coagulation pathway.*
- ***Isolated prolongation of aPTT (normal PT)*** may indicate:
  - *Coagulation Factor Deficiency (Factor VIII, IX, XI, XII, Prekallikrein, HMWK)*
  - *Presence of Antiphospholipid Antibodies especially Lupus Anticoagulant*
  - *Use of heparin (or contamination of sample with Heparin)*
  - *Specific coagulation factor Inhibitors (factor VIII inhibitor or Factor IX or XI (rare) inhibitor)*
- The ***presence or absence of bleeding manifestation*** even after major surgery may narrow down the differential diagnosis.

| Isolated Prolongation of aPTT with no bleeding manifestation | Isolated prolongation of aPTT with bleeding manifestation |
|---|---|
| • Specific Coagulation Factor Deficiencies<br>- *Factor XII Deficiency*<br>- *Prekallekrien*<br>- *HMW Kininogen Defect*<br>• ***Presence of Lupus Anticoagulant*** | • Specific Coagulation Factor Deficiencies<br>- *Factor VIII defect*<br>- *Factor IX defect*<br>- *Factor XI defect*<br>• Specific Coagulation Factor Inhibitors<br>- *Factor VIII inhibitor*<br>- *Factor IX inhibitor or Factor XI inhibitor* |




**363. Answer is A (Factor II Deficiency)**: *Refer text below*

***Prolongation of both PT and APPT is typically seen in deficiency of factors involved in the common pathway, namely factor II, factor V and factor X (and fibrinogen).***

*Heparin in clinical concentrations is typically associated with isolated prolongation of APTT while PT is normal because heparin acts on the intrinsic pathway. (However Heparin at very high concentrations within the sample may cause prolongation of both PT & APTT).*

| Causes of Prolonged PT and APTT |
|---|
| • *Coagulation Factor Deficiency (Factor II, V, X or fibrinogen)* |
| • *Use of oral anticoagulants (Warfarin)* |
| • *Disseminated Intravascular coagulation* |
| • *Severe vitamin K deficiency* |
| • *Liver Disease (Severe Hepatic Insufficiency)* |
| • *Heparin in sample (at high concentrations only)* |
| *(Heparin is typically associated with prolonged APTT & normal PT)* |

**364. Answer is C (Factor XII deficiency) :** *Nelson 17th/1660; See previous questions*

***Isolated prolongation of PTT* suggest a defect in the intrinsic pathway of coagulation cascade only, and leaves us with the possibility of either factor XIII deficiency or Haemophilia A (Factor VIII deificiency).**

***Absence of clinical bleeding* even after major surgery like tonsillectomy *suggests a classical deficiency of contact factor XII.***

| Isolated elongation of aPTT with bleeding manifestations | Isolated prolongation of aPTT without bleeding manifestations |
|---|---|
| Factor VIII defect | Factor XII defect |
| Factor IX defect | Prekallikrein defect |
| Factor XI defect | HMW kininogen defect |

**Non bleeding disorder / Deficiency of the contact factors**

- Contact factors function at the step of initiation of intrinsic pathway of the clotting cascade and include the following :

| Contact factors |
|---|
| Factor XII |
| Prekallikrein |
| High Molecular Weight Kininogen (HMWK) |

- Deficiency of these factors is characterized by –
  - Isolated prolonged of PTT
  - Absence of clinical bleeding
- These patients do not need treatment if major surgery is indicated.

***A paradoxical situation in which these is an extremely prolonged PTT but no evidence of clinical bleeding suggests a deficiency of contact factors.***

**365. Answer is C (Russell viper venom assay):** *Harrison 18th/464; 17th/369; Wintrobe's 12th/1447-1453; 'Clinical Anesthesia' 6th (Lippincott William's)/187, 'Complications in Surgery' by Doherty (2006)/187*

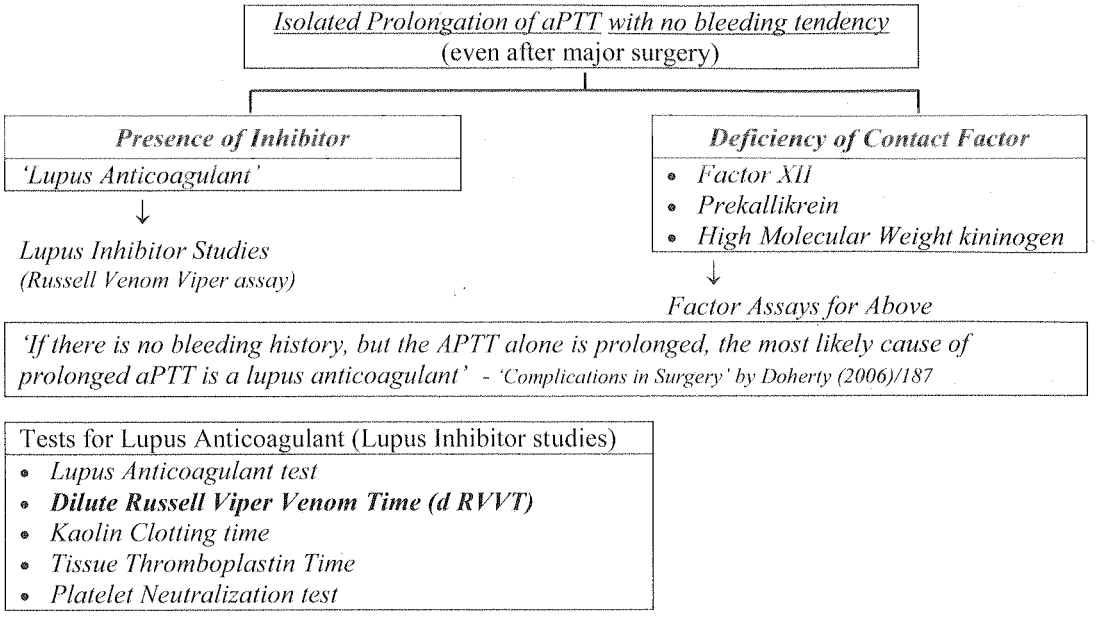
*'If there is no bleeding history, but the APTT alone is prolonged, the most likely cause of prolonged aPTT is a lupus anticoagulant' - 'Complications in Surgery' by Doherty (2006)/187*

***Russell Viper Venom assay is done to establish the presence of lupus anticoagulant and is the single best answer amongst the options provided.***

*Isolated prolongation of aPTT with no clinical history of bleeding suggests the presence of Lupus anticoagulant or deficiency of contact factors (Factor XII, Prekallikrein or HMWK)*

*No options are provided to detect deficiency of contact factors in this question and hence Russell Viper Venom assay is the answer of choice here*

***Factor VIII deficiency, Defect in platelet aggregation and vWF disease all lead to variable amount of clinical bleeding.***




**366. Answer is B (Deficiency is associated with prolonged APTT):** Harrison 18th/p 973 *Harrison's 17th/725*

***Factor VII deficiency is associated with isolated prolongation of PT, APTT is normal in Factor VII deficiency***

Genetic and laboratory characteristic of inherited coagulation disorders

| Clotting factor deficiency | Inheritance | Prevalence in General Population | Laboratory Abnormality[a] aPTT | PT | TT | Minimum Hemostatic levels | Treatment | Plasma Half-Life |
|---|---|---|---|---|---|---|---|---|
| Fibrinogen | AR | 1 in 1,000,000 | + | + | + | 100 mg/dL | Cryoprecipitate | 2-4 d |
| Prothrombin | AR | 1 in 2,000,000 | + | + | - | 20-30% | FFP/PCCs | 3-4 d |
| Factor V | AR | 1 in 1,000,000 | +/- | +/- | - | 15-20% | FFP | 36 h |
| ***Factor VII*** | ***AR*** | ***1 in 500,000*** | - | + | - | ***15-20%*** | ***FFP/PCCs*** | ***4-6 h*** |
| Factor VIII | X-linked | 1 in 5,000 | + | - | - | 30% | FVIII concentrates | 8-12 h |
| Factor IX | X-linked | 1 in 30,000 | + | - | - | 30% | FIX concentrates | 18-24 h |
| Factor X | AR | 1 in 1,000,000 | +/- | +/- | - | 15-20% | FFP/PCCs | 40-60h |
| Factor XI | AR | 1 in 1,000,000 | + | - | - | 15-20% | FFP | 40-70h |
| ***Factor XII*** | ***AR*** | ***ND*** | + | - | - | ***b*** | ***b*** | ***60 h*** |
| HK | AR | ND | + | - | - | *b* | *b* | 150 h |
| Prekallikrein | AR | ND | + | - | - | *b* | *b* | 35 h |
| Factor XIII | AR | 1 in 2,000,000 | - | - | +/- | 2-5% | Cryptoprecipitate | 11-14d |

*a* Values within normal range (-) or prolonged (+)
*b* No risk for bleeding, treatment is not indicated

HK, high-molecular weight kininogen; AR, autosomal recessive; aPTT, activated partial thromboplastin time; PT, prothrombin time; TT, thrombin time; ND, not determined; FFP, fresh frozen plasma; PCCs, prothrombin complex concentrates.

**367. Answer is A (Von Wilebrand disease):** *Hemostasis and Thrombosis: Basic Principles and Clinical Practice 5th/1155; Harrison 18th/Chapter 115*

***Von Willebrand disease (vWD) is the most common inherited bleeding disorder.***

**368. Answer is A (Hemophilia) :** *Harrison's 18th/460; Hemotasis and Thrombosis : Back Principles & clinical Practice' by Colman (Lippincott Williams) 5th/1148*

***Spontaneous Hemarthrosis and spontaneous muscle hematomas are charachteristic of moderate or severe congenital factor VIII or IX deficiency (Hemophilia).***
*Spontaneous bleeding may also be seen in Afibrinogenemia, Von willebrand disease and Scott's syndrome (defect in platelet's activated surface that promotes thrombin formation), but it is most charachteristic (Hallmark) of Hemophillia or factor VIII & IX Deficiency.*

**Bleeding Disorders**

| Spontaneous Hemarthrosis<br>Spontaneous Muscle Bleed | Spontaneous Mucosal Bleeding |
|---|---|
| • ***Spontaneous Hemarthosis and spontaneous muscle Hematomas are a hallmark of moderate or severe factor VIII and IX deficiency (Hemophilia)***<br>• *These can also be seen in moderate or severe deficiencies of other coagulation factors like fibrinogen, prothrombin and factor V, VII, & X*<br>• *These are rarely seen in other bleeding disorders.* | • Mucosal bleeding symptoms are more suggestive of underlying platelet disorders or Von Willebrand disease<br>(Disorders of primary hemostosis or platelet plug disorders) |

**Primary Hemostatic (Platelet Plug) Disorders**

| |
|---|
| **Defects of Platelet Adhesion** |
| • *Von Willebrand disease* |
| • *Bernard-Soulier syndrome (absence of dysfunction of GpIb-IX-V)* |
| **Defects of Platelet Aggregation** |
| • *Glanzmann's thrombasthenia (absence or dysfunction of GpIIbIIIa)* |
| • *Afibrinogenemia* |
| **Defects of Platelet Secretion** |
| • *Decreased cyclooxygenase activity* |
| • *Granule storage pool defects* |
| • *Non-specific inherited secretory defects* |
| • *Non-specific drug effects* |
| • *Uremia* |
| • *Platelet coating (e.g., paraprotein, penicillin)* |
| **Defect of Platelet Coagulant Activity** |
| • *Scott's syndrome* |

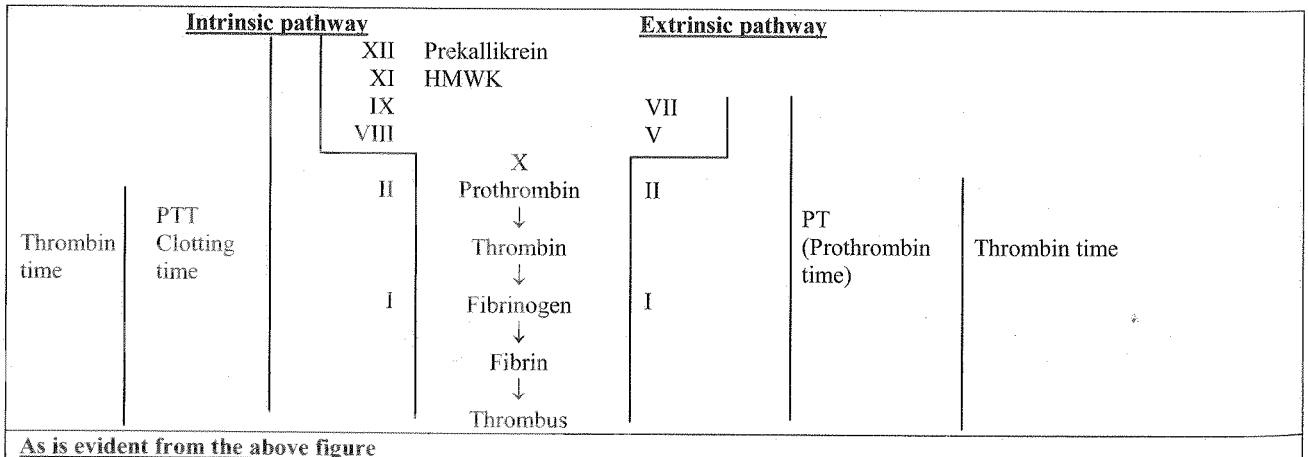
## Hemophilia

**369. Answer is B (PT is increased):** *Harrison 18th/974, 975; Harrison 17th / 726; Chandrasoma Taylor 3rd/ 428, 429*

***It is PTT which is affected (increased) and not PT (unaffected).***

Haemophilia A occurs *due to deficiency or reduced activity of factor VIII* (antihaemophilic factor). *Factor VIII is involved in the intrinsic pathway which is measured by PTT and not in extrinsic pathway which is measured as PT.*

**Understanding the coagulation cascade:**




**As is evident from the above figure**

***PTT is prolonged with deficiency of factors*** : *XII, XI, IX, VIII, II, I and Thrombin*

***PT is prolonged with deficiency of factors*** : *VII, V, II, I and Thrombin*

**370. Answer is C ( ↑ PT ) :** *Repeat AI-2001*

***Hemophilia A is associated with a defect in intrinsic pathway of clotting cascade and hence PT is essentially normal.***

**371. Answer is A (Increased bleeding time):** *Harrison 18th/p 974; Harrison 17th / 726 Chandrasoma Taylor 3rd/ 428, 429, 430; CMDT 2003 / 512; CMDT 2008/ 463, 464; CMDT 2009/478*

***Haemophilia is a disorder of coagulation (bleeding time unaffected) affecting the intrinsic pathway (prothrombin time unaffected).***

| | Haemophilia A (Classical hemophilia) | Haemophilia B (Christmas disease) |
|---|---|---|
| **Defect** | Deficiency of coagulant subunit of factor i.e (VIII c) Factor VIII = VIII c + VWF | Deficiency/absence of factor IX. |
| **Pathway of coagulation affected** | Intrinsic Pathway | Intrinsic pathway |
| **Whole blood clotting time** | ↑ | ↑ |
| **PTT** | ↑ | ↑ |
| **PT** | N | N |
| **BT** | N | N |
| **Platelet count** | N | N |
| **Tourniquet test** | N | N |

**372. Answer is A (Bleeding time) :** *Refer text below*

***Bleeding time is prolonged in von Willebrand disease, but normal in Hemophilia A***

***Both conditions present with decreased levels of factor VIII normal PT and elevated PTT and hence these features cannot be used to differentiate between hemophilia A and von Willebrand disease.***

Features of VWF and differences with Haemophilia A

| Feature | Hemophilia A | Von Willebrand Disease |
|---|---|---|
| Inheritance | Sex linked | Autosomal (Most common is A.dominant) |
| Factor VIIIc | Decreased | Decreased |
| VWF | Normal | Decreased |
| Ristocetin cofactor | Normal | Decreased |
| Common Presentation | Features of clotting disorder Skin/Mucosal bleeding – Hemarthrosis ++ | Features of bleeding disorder ± clotting disorder Skin/Mucosal bleeding + Hemorthrosis+ |
| Bleeding Time | Normal | Prolonged |
| APTT | Prolonged | Prolonged (may be normal) |
| PT | Normal | Normal |
| Thrombin Time | Normal | Normal |
| Fibrinogen | Normal | Normal |
| Platelet aggregation in Response to Ristocetin | Normal | Decreased |

**373. Answer is C (<5%):** *Primer on the Rheumatic Diseases (Springer, 2008)/471*

***Recurrent Spontaneous Hemarthrosis is commonly seen in patients with Hemophilia when factor VIII levels are less than 5 percent of normal (Moderate; Moderately severe form).***

| Classification | Levels of factor VIII | Implications |
|---|---|---|
| Mild | 6-36 % of Normal (>5%) | Bleeding generally occurs in response to mild trauma |
| Moderate | 2-5% of normal (<5%) | Associated with spontaneous bleeding. Recurrent Hemarthrosis is the most common manifestation |
| Severe | <1% of normal | Life threatening Bleeding manifestations may be seen |

**374. Answer is A (Recurrent Hemarthrosis):** *Harrison 18th/ 975; Primer on the Rheumatic Diseases (Springer, 2008)/471*

***Recurrent Hemarthrosis is the most common manifestation of Hemophilia A.***

*'Recurrent Hemarthrosis is the most common manifestation of Hemophilia-A occurring in up to two third of patients' – Primer on the Rheumatic Diseases*

*'In the severe form the most common bleeding manifestations are the recurrent hemarthroses' – Harrison*

**375. Answer is A (Osteoporosis and Restricted Joint Movement):** *Orthopaedic Surgery in Patients with Hemophilia (Springer, 2008)/263*

***The most common cause of fractures in patients with haemophilia is osteoporosis and restricted joint movements (from haemophilic arthropathy).***

*'Fractures may occur frequently and after trivial trauma because of poor musculature, osteoporosis, limited range of motion in affected joint and haemophilic changes in the bone'.*

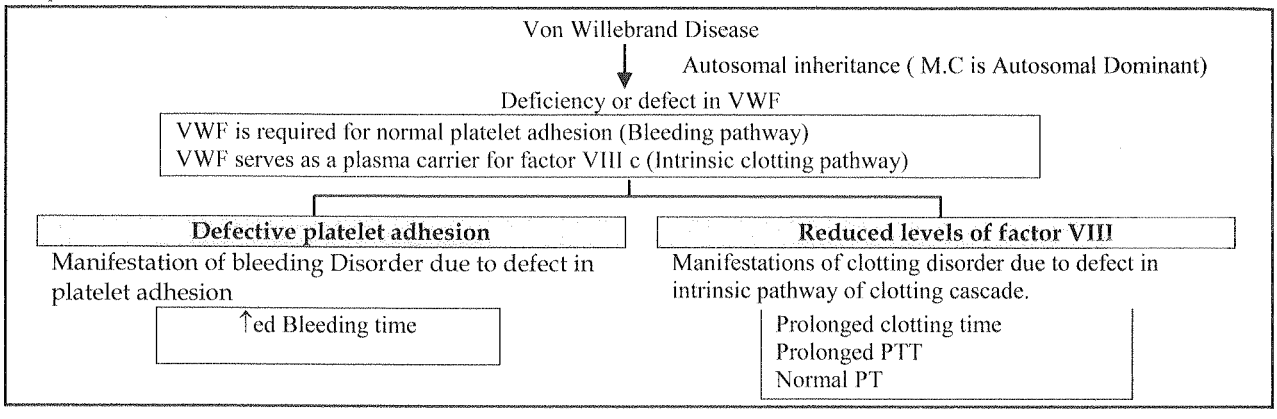
**376. Answer is B (Extraction should be done under General Anaesthesia):** *Harrison 17th/727; Lee's Synopsis of Anaesthesia 12th/422& 420, 752*

*'In dentistry Surgery, General Anaesthesia is contraindicated in patients with Hemophilia' - Lee's*

## Von Willebrands Factor (VWF) Disease

**377. Answer is A (Isolated prolonged PTT with a normal PT):** *Refer previous questions*

*Von Willebrand disease is characterized by prolonged bleeding time and a prolonged PTT. The prothrombin time is normal.*



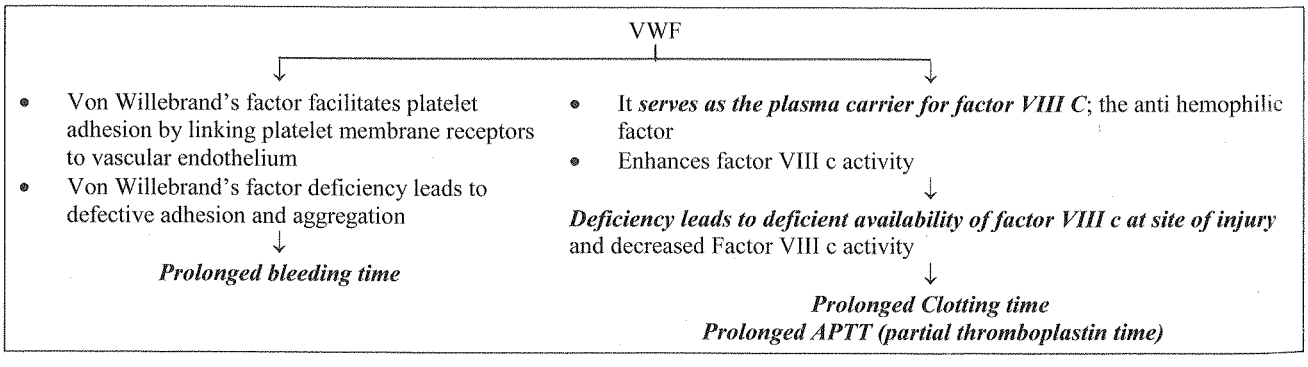

**378. Answer is D (↑PTT; Normal PT; ↑BT; ↑CT):** *Refer Notes on Von Willebrand Disease*

*Von Willebrand Disease is associated with Prolonged APTT and a Normal PT. The bleeding time (BT) and Clotting Time (CT) are both prolonged.*

**379. Answer is C (Increased platelet aggregation in response to Ristocetin):** *Read text below.*

*Von Willebrand disease is characterized by decreased (impaired) platelet aggregation in response to Ristocetin.*

*Deficiency of Factor VIII is characteristic of hemophilia and not VWF disease.* ***VWF however serves as a carrier for factor VIII c and its deficiency therefore leads to decreased availability of factor VIII c at the site of injury.*** *Decaresed level of factor VIII c in the circulation may therefore be explained by a deficiency of vW factor.*




*In vitro platelet aggregation is tested by addition of ristocetin an antibiotic. Ristocetin test is used for diagnosis of VWF disease by demonstrating decreased aggregation.*

**380. Answer is None (All statements are true):** *Read text below*

***Von Willebrand disease is associated with decreased levels of VWF and factor VIII in circulation. Bleeding time and APTT are prolonged. Platelet aggregation in response to ristocetin is abnormal which indicates a deficit in VWF or Ristocetin cofactor.***

**Von Willebrand**

Von Willebrand disease is caused by a defect of deficiency of VWF factor and presents as bleeding and coagulation disorder.

VWF factor is required fir normal platelet adhesion and aggregation.
VWF factor is the plasma carrier for factor VIII which is required for intrinsic pathway of the coagulation cascade.

Von Willebrand Factor (VWF)

VWF is essentially composed of the following components

**Factor VIII – VWF antigen**

- This antigen binds factor VIII and acts as a carrier for factor VIII in the plasma.
- It protects factor VIII from rapid proteolytic destruction in plasma

↓ Defect in VWF (VW disease) will result in

- Decreased levels of factor VIII$^{Q}$
- Decreased activity of factor VIIIc$^{Q}$

↓

- Defect in intrinsic pathway of coagulation cascade
- Prolonged PTT$^{Q}$
- PT is normal as there is no defect in extremely pathway$^{Q}$

This antigen also acts as a mediator for initial adhesion of platelets to the vessel wall.

↓ Defect in VWF will result in

Defect in platelet function (Decreased Adhesion)

↓

Prolonged bleeding time$^{Q}$

**Risocetin cofactor (VWF activity)**

↓

This cofactor is required for ristocetin induced platelet aggregation

Ristocetin is an antibioctic that induces platelet aggregation

↓ Defect in VWF activity will result in

Impaired platelet aggregation in response to Ristocetin$^{Q}$

**381. Answer is C (Von Willebrand disease):** *Harrison's 17th/725,726; Clinical Hematology 4th/381; Nelson's 17th/1660*

***Bleeding into joints along with normal PT and prolonged APTT in a girl/female suggest a diagnosis of Von Willebrand disease***

*Bleeding into joints along with prolonged APTT and normal PT may be seen in Factor VIII deficiency (Hemophilia A) and Von Willebrand disese.*

***Hemophilia** A is an X Linked disorder that affects only boys and men (Women who carry a single mutated gene are asymptomatic). The patient in question is a seven year old **girl** and is hence unlikely to have hemophilia A.*

***Von Willebrand Disease** is an Autosomally inherited condition and may affect both boys and girls. This condition may present with bleeding into joints and is associated with prolonged APTT and normal PT. VWF disease is therefore the single best answer of choice*

**Von Willebrand disease and Hemophilia A may both present with bleeding into joints, prolonged APTT and normal PT BUT Hemophilia A is a sex linked disorder that primarily involves males /boys alone.**

**Features of VWF and differences with Haemophilia A**

| Feature | Hemophilia A | Von Willebrand Disease |
|---|---|---|
| Inheritance | ***Sex linked*** Clinical disease limited to Men /boys ***(Extremely rare in females)*** | ***Autosomal (Most commonly A-dominant)*** Clinical disease may be seen in both boys & girls |
| Factor VIIIc | Decreased | Decreased |
| VWF | Normal | Decreased |
| Ristocetin cofactor | Normal | Decreased |
| Common Presentation | Features of clotting disorder Skin/Mucosal bleeding – ***Hemarthrosis ++*** | Features of bleeding disorder ± clotting disorder Skin/Mucosal bleeding + ***Hemarthrosis+*** |
| Bleeding Time | Normal | Prolonged |
| ***APTT*** | ***Prolonged*** | ***Prolonged (may be normal)*** |
| ***PT*** | ***Normal*** | ***Normal*** |
| Thrombin Time | Normal | Normal |
| Fibrinogen | Normal | Normal |
| Platelet aggregation in Response to Ristocetin | Normal | Decreased |

**Factor VII deficiency is associated with an isolated prolongation of PT (APTT is normal)**

| Causes of isolated prolongation of PT (CMDT): |
|---|
| *Factor VII deficiency* |
| *Vitamin K deficiency* |
| *Warfarin therapy* |
| *Liver disease* |

**Factor XII deficiency may present with an isolated prolongation of APTT (normal PT) but this condition is not associated with clinical Bleeding tendencies (Nelson/Clinical Hematoloy)**

*'Factor XII deficiency is a rare hereditary defect of coagulation factors in which no clinical bleeding tendancies are apparent' - Clinical Hematology*

| Isolated elongation of APTT with bleeding manifestations | Isolated prolongation of APTT without bleeding manifestations |
|---|---|
| *Factor VIII defect* | *Factor VII defect* |
| *Factor IX defect* | *Prekallekrein defect* |
| *Factor XI defect* | *HMW Kininogen defect* |

**382. Answer is C (BT + APTT + vWF-ristocetin factor assay):** Harrison 18th/p 973, 974 *Refer previous question*

***Estimation of BT, APTT and VWF-Ristocetin factor assay would provide the maximal information to aid a diagnosis of VWF disease (amongst the options provided)***

**383. Answer is C (Autosomal dominant):** Harrison 18th/p 971 *Harrison 15th/ 747; Harrison 16th/676; Harrison 17th / 723; CMDT 2008/461*

***There are 3 major forms of Von WilleBrand's disease and with one exception i.e. type III all forms are inherited as autosomal dominant trait- Harrison 16th/676***

**Von WilleBrand's disease** is the most common hereditary coagulation disorder characterized by a quantitative or qualitative defect in Von Willebrand's factor

Factor VIII circulates in blood as a complex with vWF

| Property | VWF | Factor VIII |
|---|---|---|
| **Gene** | Located on ♀ chromosome XII | Located on ♀ X chromosome |
| **Inheritance** | Autosomal dominant ♀ | Sex linked ♀ |
| **Synthesis** | Endothelial cells, megakaryocytes platelets (not in liver cells) ♀ | In liver cells ♀ |
| **Function** | Facilitate the adhesion of platelets to subendothelial collagen | Activation of factor X in coagulation cascade. |
| **Disease** | V. W. disease | Hemophillia |

## Platelet Function Disorders

**384. Answer is E (Weber-Christian disease):** *Harrison 18th/971; Harrison 17th/719, 723; 'Platelet' 2nd/826*

***Weber Christian Disease is not an inherited disorder of platelet function.***

*Weber Christian Disease is a relapsing febrile nodular non suppurative panniculitis characterized by multiple recurrent subcutaneous nodules, with accompanying fever. The laboratory abnormalities include elevated ESR, Anemia, Leucopenia or leucocytosis, depression of complements and evidence of circulating immune complexes.*

Classification of congenital disorder of platelet function:

1. Defects in platelet-vessel wall interaction (disorders of adhesion)
   - ***(a) von Willebrand disease (deficiency or defect in plasma vWF)***
   - ***(b) Bernard-Soulier syndrome (deficiency or defect in GPIb)***
2. Defects in platelet-platelet interaction (disorders of aggregation)
   - *(a) Congenital afibrinogenemia (deficiency of plasma fibrinogen)*
   - ***(b) Glanzmann thrombosthenia (deficiency or defect in GPIIb-IIIa)***
3. Disorders of platelet secretion and signal transduction
   - *(a) Storage pool deficiency*
   - *(b) Quebec platelet disorder*
   - *(c) Chediak Higashi syndrome*
   - *(d) Gray Platelet syndrome*
   - ***(e) Wiskott-Aldrich syndrome***
4. Disorders of platelet coagulation – protein interaction
   - *(a) Defect in facor Va-Xa interaction on platelets (Scott syndrome)*

**385. Answer is B (Autosomal Recessive):** *Harrison 17th/2060; Hoffman 4th/847*

***Wiskot Aldrich syndrome is an X linked Recessive syndrome and not an autosomal recessive syndrome.***

Wiskott Aldrich Syndrome (WAS)
(X linked Recessive inheritance)

**Characteristic Triad**

| Eczema | Thrombocytopenia | Immunodeficiency |
|---|---|---|
| Eczematoid Rash | Repeated Bleeding episodes<br>Platelet in WAS<br>• ↓ed Platelet count (Thrombocytopenia)<br>• ↓ed Platelet size (characteristic) (Number and morphology of Megakaryocytes in marrow is normal)<br>• Impaired platelet aggregation response | Repeated Infections<br>Immunodeficiency in WAS<br>• ↓IgM<br>• ↑IgE<br>• IgA and IgG are usually normal<br>• ↓ antibody response to uncongugated polysachharide antigens and protein antigens<br>• ↓ T cell (Acquired T deficiency) (eventually acquire severe T cell deficiency) |

**Wiskott Aldrish Syndrome is associated with an impaired platelet aggregation response.**

*'Several platelet abnormalities have been reported in Wiskott Aldrich syndrome including impaired aggregation responses'- 'Hemostasis & Thrombosis' 5th/967*

**386. Answer is A (Wiskott Aldrich syndrome):** *Harrison 17th/2060; Hoffman 4th/847*

***Thrumbocytopenia, Eczema and Recurrent Infections (Immunodeficiency) represents the charachteristic triad of Wiskott – Aldrich syndrome.***

**387. Answer is A i.e. (Autosomal Recessive disorder):** *Harrison's 17th/ 2060; Hoffman's 4th/847*

***Wiskott-Aldrich syndrome is an X-Linked Recessive Syndrome and not an Autosomal Recessive disorder***

*Eczema, Thrombocytopenia and Impaired Platelet Aggregation response are typical presenting features of Wiskott-Aldrich syndrome (Refer table in previous question).*

**388. Answer is D (Wiskott Aldrish Syndrome):** Harrison 18th/p 2702, 2703 *Hoffman 4th/848; Harrison 17th/2060*

***Small sized platelet is a characteristic feature of Wiskott Aldrich Syndrome.***

*'Platelet size is characteristically small, a feature that is highly specific for Wiskott Aldrich Syndrome' -Hoffman 4th/848*
*'Platelets in Wiskott Aldrich Syndrome are small and have a reduced half life' – Harrison*

Platelets in Wiskott Aldrich Syndrome

- ↓ed Platelet count (Thrombocytopenia)
- ↓ed Platelet size (characteristic)
  (Number and morphology of Megakaryocytes in marrow is normal)
- Impaired platelet aggregation response

**389. Answer is A (Ristocetin Aggregation is normal):** *Harrison 16th /678; CMDT 2006/525; 2008/463; 2009/476*

***'Bernard – Soulier platelets react normally to all stimuli except Ristocetin'*** *– Harrison 16th / 678*
***'Platelet aggregation is normal in response to standard agonists (Collagen,ADP,Thrombin), but platelets fail to aggregate in response to ristocetin'*** *– CMDT 2006 / 525*

**Intrinsic platelet defects to adhesion and aggregation.**

Platelet adhesion and aggregation are modulated by glycoprotein receptors located on platelet surface.

| GpIb / Ix | GpIIb / IIIa complex |
|---|---|
| • Mediates ***platelet adhesion*** | • Mediates ***platelet aggregation*** |
| • *VWF facilitates* platelet adhesion by binding to this receptor | • *Fibrinogen facilitates* platelet aggregation via sites on this receptor |

Loss or defect in above glycoprotein receptors leads to rare platelet disorders causing bleeding

**Bernard Soulier Syndrome**

- Autosomal recessive disorder
- Deficiency / dysfunction of Gp Ib / Ix Receptor
- ***Platelets cannot adhere*** to subendothelium because of lack of above receptors for VWF which mediates platelet adhesion
- ***Platelet aggregation to largely normal platelet aggregation is normal in response to standard agonists (collagen ADP, thrombin / but platelet fail to aggregate in response to ristocetin as it acts by a different mechanism***

Other laboratory parameters

- ***Thrombocytopenia may be present***
- ***Platelets on smears are abnormally large***
- Bleeding time is abnormally prolonged
- VWF factor levels in plasma are normal

Clinical presentation

- Recurrent episodes of severe mucosal haemorrhage

**Glanzmann's thrombasthenia**

- Autosomal recessive disorder
- Deficiency / dysfunction of Gp IIb / III a complex
- ***Platelets cannot aggregate*** because of lack of above receptors for fibrinogen which form the bridges between platelets during aggregation.
- ***Platelet aggregation is largely abnormal. Platelet fail to aggregate in response to standard agonists, (ADP, collagen, thrombin) as these require fibrinogen binding, but aggregate normally to ristocetin as it cause platelet clumping by a different mechanism.***

Other laboratory parameters

- Platelet number is usually normal
- Platelet morphology is usually normal
- Bleeding time is abnormally prolonged
- VWF factor level in plasma are normal

Clinical presentation

- Recurrent episodes of severe mucosal hemorrhage

**Note :Von Willebrand's disease** : ***Platelet aggregation studies with standard agonists ADP, collagen, thrombin are normal but platelet aggregation in response to ristocetin may be subnormal (CMDT 2006 / 524).***

## Thrombocytopenia and Purpura

**390. Answer is A (H. S. Purpura):** Harrison 18th/p 2797 *Harrisons 16th/ 341 t; Harrisons 17th/ 2128; API 8th /839 Chandrasoma Taylor 3rd/ 427*

***H. S. Purpura is characterized by bleeding tendency due to vasculitis. Thrombocytes remain unaffected.***

**Thrombocytopenia**

**Decreased Production**

Associated with Reduced (or absent) megakaryocytes in bone marrow
(Amegakaryocytic Thrombocytopenia)

Causes

1. Aplastic anemia *PNH*
2. Marrow infiltration
   -Leukemia
   -Metastasis
   -Radiation
3. Vitamin B12 & Folic acid deficiency (associated Megaloblastic anemia)
4. Hereditary: Autosomal dominant form of Wiskott Aldrich syndrome

Increased Destruction

Associated with normal or increased number of megakoryocytes in bone marrow
(Megakaryocytic thrombocytopenia

Causes

*Immune mechanism*

1. *ITP* Q
2. *SLE* Q
3. *Post transfusion* Q
4. Neonatal: due to maternal IgG antibodies
5. *Drugs* Q :
   - Quinine
   - Gold
   - Sulfonamides

*Non-Immune (↑consumption)*

1. TTP (↑consumption)
2. HUS
3. *DIC* Q
4. Valve prosthesis
5. Hypersplenism

**391. Answer is C (Aplastic Anemia):** *Harrisons 16th/674,341; Refer previous question*

*Amegakaryocytic Aplastic anemia is characterized by decreased or absent megakaryocytes (platelet precusors) and indicates a defect in production of platelets.*

***Amongst the options provided only aplastic anemia is associated with decreased production of platelets and causes amegakaryocytic thrombocytopenia.***

*The most common causes of thrombocytopenia with decreased number of megakaryocytes in marrow are aplastic anemia, marrow fibrosis and infiltration of marrow with malignant cells (Harrison)*

**392. Answer is A (Henoch Schonlein Purpura):** Harrison 18th/p 2797 *Harrison 16th/ 341, 17th / 2128; API 8th /839, Chandrasoma Taylor 3rd/427*

***The mechanism of ecchymosis or purpura in Henoch Schonlein is vasculitis. There is no thrombocytopenia. All other options are known causes of thrombocytopenia.***
*For details on Henoch Shonlein purpura refer the chapter on 'Connective tissue and metabolism'.*

**393. Answer is A (H. S. Purpura):** Harrison 18th/p 2797 *Harrison 17th / 2128; API 8th /839, Chandrasoma Taylor 3rd/427; Refer previous table*

***The mechanism of ecchymosis or purpura in Henoch Schonlein is vasculitis. There is no thrombocytopenia. All other options are known causes of thrombocytopenia.***

**394. Answer is D (All of the above):** *Lecture notes in Hematology 7th/168; Wintrobe's 11th/*

***SLE CLL and HIV may all cause autoimmune destruction of platelets or immune thrombocytopenia***

Cause of Autoimmune Thrombocytopenia

| Idiopathic | Secondary |
|---|---|
| Immune Thrombocytopenic purpura (ITP) | • Connective tissue disorders (Specially SLE)<br>• Lymphoproliferative disorders (Lymphoma, CLL)<br>• Infections (example HIV infection)<br>• Drugs<br>• Solid tumors |

**395. Answer is A (SLE):** *Harrison 16th / 341; (Refer Previous table)*

***SLE is characterized by antiplatelet antibody mediated autoimmune destruction of platelets.***

**396. Answer is A (Thrombocytopenia) :** *Harrison 18th/421; Harrisons 16th/ 309; Harrison 17th/ 334*

*'Thrombocytopenia is associated with non palpable purpura'. – Harrison 16th/309*

**Causes of palpable purpura :**

| Emboli (bacterial fungal or parasitic) | Vasculitis |
|---|---|
| Acute meningococcemia<br>Disseminated gonococcal infection$^{Q}$<br>Rocky mountain spotted fever<br>Ecthyema gangrenosum | Leucocytoclastic vasculitis (predominantly cutaneous vasculitis)<br>Henoch – Schonlein pupura<br>Polyarteritis nodosa |

**Causes of Non palpable pupura:**

| Primary cutaneous disorders | Systemic diseases | | | | |
|---|---|---|---|---|---|
| | *Clotting disturbance* | *Vascular fragility* | *Thrombosis* | *Emboli* | *Possible immune complex* |
| Trauma<br>Solar purpura<br>Steroid purpura<br>Capillaritis<br>Livedoid vasculitis | Thrombocytopenia (including ITP)<br>Abnormal platelet function<br>Clotting factor defects | Amyloidosis<br>Ehlers-Danlos syndome<br>Scurvy | Disseminated intravascular coagulation<br>Monoclonal cryoglobulinemia<br>Thrombotic thrombocytopenic purpura<br>Warfarin reaction | Cholesterol<br>Fat | Gardner-Diamond syndrome<br>Waldenstrom's hypergammaglobulinemic purpura |

**397. Answer is C (H. S. Purpura):** Harrison 18th/p 422, 2797 *Harrison 16th/ 309; Harrison 17th/ 335, 2128*

***Henoch Sconlein Purpura is associated with palpable purpura*** *without thrombocytopenia*$^{Q}$

## Idiopathic Thrombocytopenic Purpura (ITP)

**398. Answer is C (Antibody to platelets):** *Harrison 17th / 721; Chandrasoma Taylor 3rd/ 425, Robbins 6th/ 635-636, 7th/ 651*

***'There are two clinical subtypes of primary ITP, acute and chronic, both are autoimmune disorders in which platelet destruction results from the formation of antiplatelet antibodies'*** *– Robbins 7th/ 651*

***Idiopathic thrombocytopenic purpura*** *is a disease characterized by severe reduction of platelet numbers, caused by immune destruction of platelets. The mechanism of ITP appears to be immune complexes containing antibodies which react with platelets and lead to their immunological destruction.*

**399. Answer is A (Splenomegaly):** *Robbins 7th/651,652; Ghai 6th/324*

***Splenomegaly and lymphadenopathy are rare in primary Idiopathic Thrombocytopenic purpura and their presence should lead one to consider other possible diagnosis*** *– Robbins*

Immune Thrombocytic Purpura (ITP)
*(Idiopathic Thrombocytopenic Purpura)*

Autoimmune Antibodies against Platelets

From response to ***previous viral infection***$^{Q}$ (Acute ITP) or From underlying immune dysregulation (chronic ITP)

↓

*Platelet destruction*

Thrombocytopenia

**Clinical manifestations**

Clinical signs and symptoms of ITP are reflective of thrombocytopenia (Bleeding manifestations due to decreased platelet count)

| **Characteristic Clinical Features** | ***Clinical features that are characteristically unusual and suggest the possibility of other diagnosis*** |
|---|---|
| Bleeding and haemorrhages from small venules or capillaries<br>• *Spontancouspetechiae*<br>• *Spontaneous echymoses*<br>• *Spontancous mucosal bleeding*<br>• *Easy Bruisibility*<br>• *Spleen is normal in size* | • *Frequent Bleeding and haemorrhages from larger veins and arteries and bleeding into joints (Suggest coagulation disorders)*<br>• *Splenomegaly and Lymphadenopathy are unusual/rare and their presence should lead one to consider other diagnosis.* |

**Laboratory Features**

- Isolated thrombocytopenia
- Platelet Antibodies
- Normal or increased number of megakaryocytes on bone marrow examination

Features of bleeding disorder

- Bleeding time is prolonged
- Tests of coagulation are essentially normal
  - Normal PT
  - Normal APTT
  - Normal Fibrinogen
  - Normal Fibrinogen Degradation products
  - Normal levels of coagulation factors

*'Hepatomegaly, splenomegaly and lymphadenopathy are notably absent in ITP, and their presence should initiate an investigation for other possible underlying illnesses associated with thrombocytopenia'- Oski's 2nd/463*

**400. Answer is B (Massive splenomegaly) :** *Refer Previous Question*

***Immune Thrombocytopenic Purpura is not associated with massive splenomegaly***

*'Hepatomegaly, splenomegaly and lymphadenopathy are notably absent in ITP, and their presence should initiate an investigation for other possible underlying illnesses associated with thrombocytopenia'- Oski's Essential Pediatrics 2nd/463*

**Acute ITP is considered a self limiting condition**

*'Immune Thrombocytopenic purpura is a self limiting condition and most children will have normal platelet count within 8-12 weeks even without treatment' – 'Pediatrics: A concise Text' by Kabro & Srivastava 1st/164*

*'Acute ITP in children frequently has a benign course with an excellent prognosis. More than 50% of untreated children with ITP recover within 4 weeks without treatment and more than 80% recover 6 months' – Oski's 2nd/463*

**Intravenous immunoglobulins may be required for treatment of ITP**

*'Intravenous Immunoglobulin is a useful modality for treatment of ITP' -Oski's 2nd/464*

| **Common Treatment Modalities for ITP** *(Platelet count <20,000/μl or significant mucosal bleeding)* |
|---|
| • *Corticosteroids*<br>• *IV Immunoglobulins / gamma globulins*<br>• *Additional Immunosupressive agents (Rituximab / Anti CD 20 Antibody)*<br>• *Splenectomy* |

**401. Answer is A (Bleeding into joints is a common manifestation):** *Robbins 7th/651,652; Ghai 6th/329*

*The patient in question is presenting with Acute Idiopathic Thrombocytopenic Purpura (ITP) Bleeding into joints is an uncommon manifestation of ITP.*

***Bleeding into joints is commonly seen in coagulation disorders and not in bleeding disorders (platelet disorders) like ITP***

*Thrombocytopenia, increased number of megakaryocytes and spontaneous remission in 80% of cases are characteristic features of Acute ITP.*

Features of Acute ITP

| Characteristics | Feature |
|---|---|
| Peak Age incidence | 2-6 years |
| Sex predilection | None |
| Presenting features | • *Preceding/Antecedent viral infection seen in about 50% of cases*<br>• *Bleeding from mucosal surfaces with frequent petichea and echymoses*<br>***Bleeding into joints is unusual***<br>• Spleen is normal is size<br>***No Hepatosplenomegaly or Lymphadenopathy*** |
| Laboratory features | • ***Thrombocytopenia***<br>• Platelet Antibodies (Antibodies against platelets)<br>• ***Normal or Increased megakaryocytes in marrow***<br>• Prolonged Bleeding time<br>• Normal tests for Coagulation<br>- PT Normal<br>- PTT Normal<br>- Fibrinogen Normal<br>- FDP Normal<br>- Coagulation factors Normal |
| Course and Prognosis | Self Limiting Course<br>***Spontaneous remission is seen in 80% of cases in 4-6 weeks*** |

**402. Answer is C (Spontaneous remission is common in chronic ITP):** *Ghai 6th/324; Wintrobe's 11th/1534*

***Spontaneous remission is common in Acute Form of ITP but it is an uncommon feature of chronic ITP***

**Idiopathic/immune Thrombocytopenic purpura**

ITP occurs in two forms, namely acute ITP and chronic ITP
Acute ITP and chronic ITP differ in incidence, prognosis and therapy

Features of Acute and Chronic Idiopathic Thrombocytopenic Purpura (ITP)

| Features | Acute ITP | Chronic ITP |
|---|---|---|
| Peak age of incidence | Children, 2-6 yr | Adults 20-40 yr |
| Sex predilection | None | 3:1 female to male |
| Antecedent infection | Common 1-3 wk before | Unusual |
| Onset of bleeding | Abrupt | Insidious |
| Hemorrhagic bullae in mouth | Present in severe cases | Usually absent |
| Platelet count | <20,000 / µl | 30,000-80,000/µl |
| Eosinophilia and lympocytosis | Common | Rare |
| Duration | 2-6 wk; rarely longer | Months or years |
| Spontaneous remission | Occur in 80% of cases | Uncommon |

**403. Answer is C (Bleeding time):** Harrison 18th/p 460 *Harrison 17th / 366; See text below*

*Bleeding time is indicative of function of platelets.* ***In any form of thrombocytopenia it is platelets that are affected and hence the deranged parameter would be bleeding time.***
PT, APTT and Clotting time are parameters of coagulation disorders and not bleeding disorders. These parameters will be normal in disorders of platelet function.

**404. Answer is B (Immunogenic Thrombocytopenia):** Harrison 18th/p 968 *Harrison 15th/ 747; Harrisons 16th/675; Harrison 17th / 722*

*Immunogenic thrombocytopenias are caused by immune mediated destruction of platelets and therefore platelet supplementation is unlikely to benefit.*

**Hemorrhage in a case** of immunogenic thrombocytopenia such as Idiopathic Thrombocytopenic Purpura (ITP) is **controlled by** -

- Glucocorticoids
- Intravenous Immunoglobulins
- Splenectomy

## Thrombotic Thrombocytopenic Purpura (TTP)

**405. Answer is C (Hypertension):** *Harrison 18th/969, 970; 16th/678, 679; 17th / 722, 723; CMDT 2008/459; CMDT 2009/472*

*Blood pressure is normal in Thrombotic Thrombocytopenic purpura.*

**Thrombotic Thrombocytopenic purpura** is a disorder of 'vessel wall' Q characterised by lesions in arteriolar walls Q in various organs that initiate formation of **localised platelet thrombi and fibrin deposits at various sites.**

**Clinical Pentad of TTP**

| | | | | |
|---|---|---|---|---|
| **Microangiopathic Hemolytic Anemia** Q (Coomb's negative)<br>- Haemolysis Q<br>- Fragmentation Q of RBC's<br>- Increased LDH (elevated due to intra- vascular hemolysis) Q | **Thrombocytopenia** Q (due to consumption of platelets) | **Decreased Renal Function** Q (due deposits in the Renal Vasculature.) | **Disturbed Neurological function** Q<br>Characteristically diffuse and non focal eg.<br>- Confusion<br>- Aphasia<br>- Alteration in consciousness | **Fever** |

**Tests of coagulation are essentially normal** Q

- Normal PT Q
- Normal APTT Q
- Normal Fibrinogen concentration Q
- Normal Fibrin degradation Products Q

***Thus: PENTAD as mentioned above + normal coagulation tests: PATHOGNOMIC OF TTP***

**406. Answer is D i.e. (Grossly abnormal coagulation tests):** Harrison 18th/p 969 *Harrison's 17th /722, 723; Refer previous question*

*Tests of coagulation are essentially normal in Thrombotic Thrombocytopenic Purpura (TTP).*

Clinical Pentad + Normal Tests for coagulation : TTP

Clinical Pentad of TTP
- *Microangiopathic Hemolytic Anemia*
- *Thrombocytopenia*
- *Decreased Renal function*
- *Disturbed Neurological function*
- *Fever*

**407. Answer is D (Thrombocytopenia, anemia, neurological abnormalities, progressive renal failure and fever)**

***Thrombotic Thrombocytopenic Purpura (TTP) is characterized clinically by the Pentad of Microangiopathic Hemolytic Anemia, Thrombocytopenia, Decreased Renal Function, Disturbed Neurological function and Fever.***

**408. Answer is C (Hypertension):** *Refer Previous question*

*Hypertension is not a typical feature of TTP.*

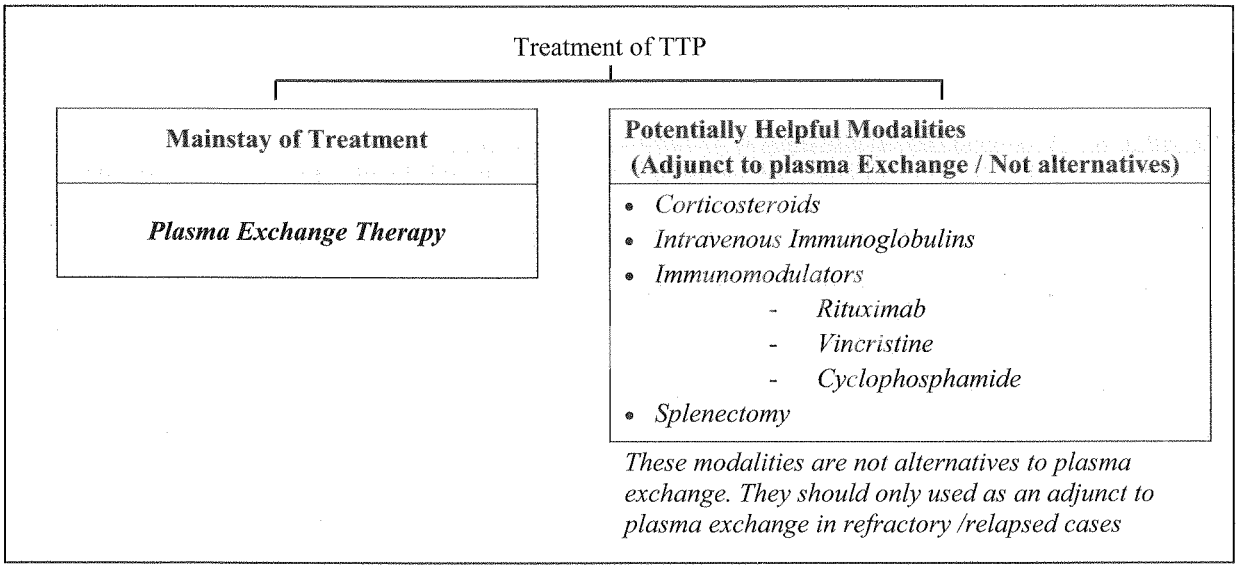
*Fever, Hemolysis (microangiopathic intravascular hemolysis) and Low platelet count (Thrombocytopenia) are part of the 'pentad' of TTP*

**409. Answer is A (Plasma Exchange Therapy):** *Harrison 18th/p 970 Harrison's 17th/ 723*

*Plasma Exchange Therapy is the treatment of choice for TTP.*

*Pentad of Fever, Microangiopathic Hemolytic Anemia, Thrombocytopenia (platelets count = 20,000), Renal Failure (↑serum creatinine) and Neurological dysfunction (altered consciousness) together with normal tests of coagulation (normal PT and aPTT) confirms a diagnosis of Thrombotic Thrombocytopenic Purpura. Plasma Exchange forms the mainstay of treatment of TTP.*

*'Plasma Exchange remains the mainstay of treatment of TTP' – Harrison's 17th/723*




**410. Answer is D & E (Heparin & Platelet transfusion):** *'The Cleveland Clinic Internal Medicine Case Review' (2003)/153*

*Heparin and platelet transfusions are not used in the treatment of Thrombotic Thrombocytopenic Purpura*

**Heparin and platelet transfusions are not used in treatment of TTP**

*'Heparin is not indicated in the treatment of TTP-HUS. Platelet transfusion is also not indicated and may worsen neurological symptoms and renal dysfunction. Platelet transfusion can lead to the geeration of new or expanding thrombi, as the infused platelets are transfused'* - *Cleveland Clinic Internal Medicine Case Reviews (2003)/153*

**Plasmapharesis, Corticosteroids and Immunotherapy may be used in treatment of TTP**

*Plasmapharesis forms the mainstay of treatment for TTP. Corticosteroids and Immunotherapy may be used as adjuncts to plasma exchange in refractory /relapsed cases.*

## Disseminated Intravascular Coagulation (DIC)

**411. Answer is D (All of the above):** Harrison 18th/p 978 *Harrison 17th/34*

*DIC may be associated with all of the options provided in the question.*

Common Clinical causes of Disseminated Intravascular Coagulation:

| Sepsis | Immunologic disorders |
|---|---|
| • Bacterial<br>• Staphylococci, streptococci, pneomococci, meningococci, gram-negative bacilli<br>• Viral<br>• Mycotic<br>• Parasitic<br>• Rickettsial | • Acute hemolytic transfusion reaction<br>• Organ or tissue transplant rejection<br>• Graft-versus-host disease |

| Trauma and tissue injury | Drugs |
|---|---|
| • Brain injury (gunshot)<br>• Extensive burns<br>• Fat embolism<br>• Rhabdomyolysis | • Fibrinolytic agents<br>• Aprotinin<br>• Warfarin (especially in neonates with protein C deficiency)<br>• Prothrombin complex concentrates<br>• Reactional drugs (amphetamines) |
| **Vascular disorders** | **Evenomation** |
| • Giant hemangiomas (Kasabach-Merrit syndrome)<br>• Large vessel aneurysms (eg. Aorta) | • Snake<br>• Insects |
| **Obstetric complications** | **Liver disease** |
| • Abruptio placentas<br>• Amniotic fluid embolism<br>• Dead fetus syndrome<br>• Septic abortion | • Fulminant hepatic failure<br>• Cirrhosis<br>• Fatty liver of pregnancy |
| **Cancer** | **Miscellaneous** |
| • Adenocarcinoma (prostate, pancreas etc)<br>• Hematologic malignancies (acute promyelocytic leukemia) | • Shock<br>• Respiratory distress syndrome<br>• Masive trasnfusion |

**412. Answer is E (All of the above):** Harrison 18th/p 978 *Harrison 17th/729; Thrombosis and Hemmorhage 3rd/781*

*DIC may be associated with all of the options provided in the questions.*

**Note**:
*Although Lymphoma is not mentioned as a cause in Harrison's text, it is an established cause for DIC.*

**Common Neoplastic causes of DIC** - *Thrombosis & Hemorrhage 3rd/781*

| Solid Tumors | Leukemia |
|---|---|
| • Adenocarcinoma (prostate, pancreas etc)<br>• Lymphoma | • Acute Promyclocytic Leukemia (characteristic)<br>• Acute Myelogenous<br>• Chronic Myelogenous<br>• Acute Lymphoblastic<br>• Others |

**413. Answer is C (Decreased PTT):** Harrison 18th/p 979 *Harrison 17th / 729; CMDT 2003 / 516-18; 2005/511-513; 2008/467, 468; CMDT 2009/474*

*PTT is increased in DIC*

DIC or Disseminated Intravascular Coagulation, is a complex thrombohaemorrhagic disorder characterized by the following sequence of events in general :

| **Events** |
|---|
| 1. Intravascular activation of coagulation by *both intrinsic and extrinsic mechanism.* Q<br>2. A thrombotic phase<br>3. Consumption phase, wherein most coagulation factors and platelets are consumed.<br>4. Stage of secondary fibrinolysis, at site of intravascular coagulation. |
| **Laboratory findings** are in accordance with the above pathogenic mechanisms : |
| 1. *Platelets count, coagulation factors and fibrinogen level: are decreased* Q or 'consumed'. As a result of above: The *bleeding time as well as the coagulation time both are prolonged* Q therefore<br>- *PTT: increased* Q<br>- *PT: increased* Q<br>- *Thrombin time : increased* Q<br>2. Increased secondary fibrinolysis accounts for<br>- *raised plasmin levels* Q<br>- *raised levels of fibrin degradation product (FDP).* Q<br>3. The thrombolic phase accounts for *features of microangiopathic haemolytic anemia.* Q<br>- *presence of schistiocytes, spherocytes, burr cells, halmet cells in the peripheral film.* Q |

**Some question asked:**
- Most important treatment is : finding a reversible cause and *treatment of the cause* ♀
- *Finding in DIC, that correlates best and most closely with bleeding is : fibrinogen level* ♀
- Most common site for thrombin formation in DIC is : Brain ♀ (Brain > heart > lung > kidney > adrenal > liver)
- DIC is related to 2 very important endocrine manifestations :
  a. *Adrenals - Fredrich Hausen Syndrome.* ♀
  b. *Pituitary - Sheehan's Syndrome.* ♀

**414. Answer is D (Increased FDP, prolonged PT, Reduced platelets):** *Harrison 18th/p 979; 16th / 683; Harrison 17th / 729*

*The laboratory manifestation of DIC include* ***thrombocytopenia (Reduced platelets), prolonged PT****, PTT and thrombin time (TT). Reduced fibrinogen levels from depletion of coagulation protein and* ***elevated FDP*** *from intense secondary fibromolysis - Harrison*

**415. Answer is B (Serum FDP):** *Harrisons 17th/729*

*The most sensitive test for DIC is the FDP level – Harrisons*

FDP levels and DIC – Harrison
- The most sensitive test for DIC is the FDP level
- DIC is an unlikely diagnosis in the absence of normal FDP
- The D-Dimer test is a specific test for detection of FDP and indicates that the cross linked fibrin has been digested by plasmin

Note
Because fibrinogen has a prolonged half life, plasma levels diminish acultely in only severe cases of DIC.
Low fibrinogen levels predict the tendency of bleeding in DIC

♀ Most sensitive test for DIC is – Elevated FDP levels
♀ Most sensitive test for DIC that predicts tendency of bleeding in - Serum Fibrinogen levels

**416. Answer is C (Hyperfribrinogenemia):** *Harrison 18th/ 979*

*Disseminated Intravascular Coagulation (DIC) is typically associated with Hypofibrinogenemia from increased fibrinogen consumption.*

**417. Answer is C (Low serum fibrinogen level):** Harrison 18th/p 979 *Harrisons 16th/684*

*Finding in DIC that corvelates relates to bleeding tendency is serum fibrinogen levels*

*'Low fibrinogen levels predicts more bleeding'- Harrison*

**418. Answer is C (M3-AML):** *Ghai 6th/567; Repeat; Robbins*

*DIC or DIVC may occur in any subgroup of AML but is especially common in Acute Promyelocytic Leukemia or M3-AML of FAB classification.*

**419. Answer is C (Decreased coagulation factor levels):** Harrison 18th/p 969, 970, 979 *Harrison 17th / 722, 723, 729; Refer previous two questions*

*While coagulation factors are characteristically consumed (decreased) in case of DIC their levels are essentially normal in case of TTP*

## Hypercoagulable States / Thrombosis

### General

**420. Answer is B (factor V Leiden deficiency):** *Harrison 16th/342*

*Factor V Leiden mutation (or ↑ Factor V Leiden levels) are associated with a hypercoaguable state and not a Factor V Leiden deficiency.*

| Inherited |
|---|
| • Defective inhibition of coagulation factors<br>- Factor V Leiden (resistant to inhibition by activated protein C)<br>- Antithrombin III deficiency (or resistance)<br>- Protein C deficiency (or resistance)<br>- Protein S deficiency (or resistance)<br>- Prothrombin gene mutation (G20210A)<br>• Impaired clot lysis<br>- Dysfibrinogenemia<br>- Plasminogen deficiency<br>- tPA deficiency<br>- PAI-I excess<br>• Uncertain mechanism<br>- Homocystinuria |

| Acquired |
|---|
| • Diseases or syndromes<br>- Lupus anticoagulant/anticardiolipin antibody syndrome<br>- Malignancy<br>- Myeloproliferative disorder<br>- Thrombotic thrombocytopenic purpura<br>- Estrogen treatment<br>- Hyperlipidemia<br>- Diabetes mellitus<br>- Hyperviscosity<br>- Nephrotic syndrome<br>- Congestive heart failure<br>- Paroxysmal nocturnal hemoglobinuria<br>• Physiologic states<br>- Pregnancy (especially postpartum)<br>- Obesity<br>- Postoperative state<br>- Immobilization<br>- Old stage |

**421. Answer is C (Idiopathic Thrombocytopenic Purpura (ITP)):** *Harrisons 17th/367, 741*

***Idiopathic Thrombocytopenic Purpura (ITP) is an immune complex mediated thrombocytopenia characterized by varying degrees of bleeding manifestations due to destruction of platelets. ITP is not associated with an increased incidence of venous and/or arterial thrombosis.***

*Paroxysmal Nocturnal Haemoglobinuria (PNH), Diseminated Intravascular Coagulation (DIC) and Heparin Induced Thrombocytopenia (HIT) are all associated with increased risk of venous and/or arterial thrombotic events.*

**Risk factors for Thrombosis:**

| Venous | Venous and Arterial |
|---|---|
| **Inherited** | **Inherited** |
| *Factor V Leiden* | *Homocystinuria* |
| *Prothrombin G20210A* | *Dysfibrinogenemia* |
| *Antithrombin deficiency* | |
| *Protein S deficiency* | |
| *Elevated F VIII* | |
| **Acquired** | **Acquired** |
| *Age* | *Malignancy* |
| *Previous thrombosis* | *Antiphospholipid antibody syndrome (APLA)* |
| *Immobilization* | *Hormonal therapy* |
| *Major surgery* | *Polycythemia vera* |
| *Pregnancy &puerperium* | *Essential thrombocythemia* |
| *Hospitalization* | ***Paroxysmal nocturnal hemoglobinuria (PNH)*** |
| *Obesity* | Thrombotic thrombocytopenic Purpura *(TTP)* |
| *Infection* | ***Heparin-induced thrombocytopenia (HIT)*** |
| *APC resistance, nogenetic* | ***Disseminated intravascular cogulation (DIC)*** |
| **Unknown**[a] | **Mixed (Inherited and acquired)** |
| *Elevated factor II, IX, XI* | *Hyperhomocysteinemia* |
| *Elevated TAFI levels* | |
| *Low levels of TFPI* | |
| [a]Unknown whether risk is inherited or acquired.<br>***Note*** APC, activated protein C; TAFI, thrombin-activatable fibrinolysis inhibitor; TFPI, tissue factor pathway inhibitor. | |

***Note : Heparin induced Thrombocytopenia is more commonly associated with Thrombosis than Bleeding***

**Heparin induced Thrombocytopenia is more commonly associated with Thrombosis than Bleeding**

- Heparin induced thrombocytopenia should be included in the differential diagnosis of conditions that produce thrombosis despite thrombocytopenia.
- ***Despite thrombocytopenia bleeding is rare in HIT.***
  On the contrary HIT is more related to thrombosis, which often leads to initial recognition of this condition (HIT).

*'Thrombosis often leads to initial recognition of HIT. Bleeding is rare despite thrombocytopenia'*
*- Essentials of Emergency Medicine (2006)/286*

| *Thrombocytopenia with Thrombosis* |
|---|
| ***DIC*** |
| ***TTP*** |
| ***HUS*** |
| ***HIT*** |

- *Thrombosis* in Heparin Induced Thrombocytopenia is *caused by the generation of prothrombotic platelet microparticles that promote thrombin generation.*

*HIT is an antibody – mediated process that is triggered by antibodies directed against neoantigens on PF4 that are exposed when heparin binds to this protein. These antibodies (usually IgG type) bind simultaneously to heparin PF4 complex and to platelet Fc receptors. Such binding activates the platelets and generates platelet microparticles. Circulating microparticles are prothrombotic because they express anionic phospholipids on their surface and can bind clotting factors and promote thrombin generation.*

- **Features of Heparin-Induced Thrombocytopenia**

| Features | Details |
|---|---|
| *Thrombocytopenia* | *Platelet count of $\leq$100,000/$\mu$L or a decrease in platelet count $\geq$ 50%* |
| *Timing* | *Platelet count falls 5-10 days after starting heparin* |
| *Type of heparin* | *More common with unfractionated heparin than with low-molecular-weight heparin* |
| *Type of patient* | *More common in surgical patients than medical patients; more common in women than in men.* |
| *Thrombosis* | *Venous thrombosis more common than arterial thrombosis* |

**422. Answer is C (Hypomagnesemia):** *Harrison 15th/ 359, Harrison 16th/ 342; Harrison 17th/ 367*

*All conditions other than hypmagnesemia are known predisposing causes of thrombosis.*

**423. Answer is D (Dysfibrinogenemia):** *Harrison 16th/342*

*Dysfibrinogenemia is associated with a hypercoagulable state.*
*Deficiency of Protein C, Protein S and Antithrombin III are associated with hypocoagulable states and not their elevated levels (↑)*

**424. Answer is B (Leiden mutation):** *Harrison 16th/342; Refer text below*

*Hypercoagulability due to defective Factor V gene is called 'Leiden mutation' and is named after the city in which it was described.*

Factor V Leiden

- Factor V Leiden is a variant (mutated) of normal clotting factor V and differs from normal clotting factor V by a single nucleotide.
- While Factor V Leiden is completely normal in terms of its ability to prevent bleeding, the one amino acid difference makes Factor V Leiden resistant to being degraded by activated protein C and protein S.
- Consequently factor V Leiden persists in the circulation longer and contributes to formation of blood clots.
- Factor V Leiden mutation is the most common underlying genetic cause of thrombophilia (venous thrombosis)
- Factor V Leiden mutation poses a life long risk of deep venous thrombosis.

**425. Answer is C (Factor V Leiden Mutation):** *William's 7th/1984; The Five Minute Clinical Consult (2009)/470; Clinical Hematology 4th/386*

*Factor V Leiden mutation is the most common inherited thrombotic disorder*

| | | |
|---|---|---|
| *Most common genetic cause for thrombophilia* | : | *Factor V Leiden* |
| *Most common congenital cause of venous thrombosis* | : | *Factor V Leiden* |
| *Most common hereditary blood coagulation disorder* | : | *Factor V leiden* |

**426. Answer is D (Homocystenemia):** *Harrison 16th/686*

***Homocystenemia is associated with increased risk of arterial thrombosis.***

*Deficiency of AT III, Protein C and Protein S predisposes to venous thrombosis and not arterial thrombosis.*

| Abnormality | Arterial | Venous |
|---|---|---|
| Factor V Leiden mutation | — | + |
| Prothrombin | — | + |
| ***Antithrombin III*** | — | + |
| ***Protein C*** | — | + |
| ***Protein S*** | — | + |
| ***Homocysteinemia*** | + | + |
| Antiphospholipid syndrome | + | + |

**427. Answer is None or A (Infection):** *CMDT 2003 / 468 ' Principles of pharmacology' by Golan, Armstrong 2nd/397, The Washington Manual of Hematology and Oncology' (2003) / 27*

***Infection has not been mentioned as a direct cause of hypercoagulability in any standard textbook and is the single best answer of exclusion.***

| Acquired Condition | Mechanism of Hyper Coagulability |
|---|---|
| • Antiphospholipid syndrome | • Autoantibodies to negatively charged phospholipids →↑platelet adhesion |
| • Heparin-induced thrombocytopenia | • Antibodies to platelet factor 4 → platelet activation |
| • Malignancy | • Tumor cell induction of tissue factor expression |
| • ***Myeloproliferative syndromes*** | • Elevated blood viscosity, altered platelets |
| • Nephrotic syndrome | • Loss of antithrombin III in urine↑. Fibrinogen,↑ platelet activation |
| • Oral contraceptive use, estrogen replacement therapy | • ↑Hepatic synthesis of coagulation factos and/or effects of estrogen on endothelium (effect may be more prominent in patients with underlying primary hypercoagulability) |
| • Paroxysmal nocturnal hemoglobinuria | • Unknown, possibly "leaky" platelets |
| • Postpartum period /Pregnancy | • Venous stasis, increased coagulation factors, tissue trauma |
| • ***Surgery /trauma (postoperative period)*** | • Venous stasis, immobilization, tissue injury |
| • ***Inflammatory Bowel Disease*** | • Increased inflammatory mediators down regulate thrombomodulin leading to impaired generation of APC.<br>• Elevated levels of factor VIII, Fibrinogen; ↓ Protein S activity. |

***Prolonged surgery*** *has been directly mentioned in association with hypercoagulable states in some standard text books including 'Washington Manual of Hematology and Sub specialty consult'*

*Also 'postoperative state' is an established cause of hypercoagulability (CMDT) and hence prolonged surgery has been included as a correct option.*

**428. Answer is A (Diabetes Mellitus) :** Harrison 18th/p 883, 987 *Harrisons 17th / 632, 732, 660; CMDT 2008 / 468)*

***Diabetes Mellitus has not been mentioned as a risk factor for deep venous thrombosis.***

*Prolonged surgery and OCP usage are established risk factors.*
*PNH is associated with hypercoagulability (CMDT 2008) and an increased risk of deep venous thrombosis.*

| Acquired | Inherited | Mixed/Unknown |
|---|---|---|
| *Orthopedic surgery* | *Antithrombin deficiency* | *High levels of factor VIII* |
| *Neurosurgery* | *Protein C deficiency* | *High levels of factor IX* |
| ***Major abdominal surgery*** | *Protein S deficiency* | *High levels of fibrinogen* |
| *Major trauma* | *Factor V Leiden (FVL)* | *High levels of TAFI* |
| *Central venous catheters* | *Prothrombin 20210A* | *Low levels of TFPI* |
| *Malignancy* | *Non-O blood group* | *APC resistance in the absence of FVL* |
| *Antiphospholipid syndrome* | *Dysfibrinogenemia* | *Hyperhomocysteinemia* |
| *Puerperium* | *Factor XIII 34val* | *High levels of PCI (PAI-3)* |
| *Prolonged bed rest* | | |
| *Pregnancy* | | |
| *Obesity* | | |
| *Plastercast* | | |

| | | |
|---|---|---|
| ***Oral contraceptives*** | | |
| *Hormonal replacement therapy* | | |
| *Myeloproliferative disorders* | | |
| *Polycythemia vera* | | |
| *Long-haul travel* | | |
| *Age* | | |
| ***PNH** (Harrison's 17th/632)* | | |

TAFI, thrombin activable fibrinolysis inhibitors; TFPI, tissue factor pathway inhibitor; PCI, protein C inhibitor; PAI-3, plasminogen activator inhibitor-3; APC, activated protein C

**429. Answer is C (Antibodies to factor VIII) :** Harrison 18th/p 986, 987 *Harrison 16th/e 686; 17th/ 367,732,733,734; CMDT 2008/465; CMDT 2009/480*

*Antibodies to factor VIII should be suspected in a disorder presenting with 'bleeding' and not in presenting with recurrent thrombosis.*

- *'Antibodies against factor VIII should be suspected in any acquired severe bleeding disorder associated with a prolonged PTT' – CMDT*
- *Factor VIII antibodies are distinguished from lupus anticoagulant by presence of clinical bleeding.' – CMDT*

**Approach to Patient presenting with deep venous thrombosis**

Deep venous thrombosis

| | |
|---|---|
| • No clear predisposing factor<br>• Strong family history<br>• Presentation at age <30<br>• More than one episode | • Predisposing factor present<br>- During pregnancy<br>- Using oral contraceptive pills<br>- SLE etc. |
| ↓ | ↓ |
| Perform assay for | Perform assay for |
| *Antithrombin III*<br>*Protein C/s*<br>*Factor V leiden* | *Lupus anticoagulant antibodies*<br>*Factor V leiden* |

| **Major coagulation defects associated with venous thrombosis** |
|---|
| Factor V leiden (commonest association with DVT) |
| Antithrombin III deficiency |
| Protein C deficiency |
| Protein S deficiency |
| Prothrombin gene mutation |
| Homocyteinemia |
| Antiphospholipid antibody |

***Homocyteinemia and Antiphospholipid antibodies are also associated with arterial thrombi (others being associated with venous thrombosis only).***

## Antiphospholipid Syndrome

**430. Answer is A (Pancytopenia):** *Harrison 18th/987; 17th/732, 1579, 2082; API textbook Medicine 8th/306, 307*

*Venous thrombosis, recurrent abortions and pulmonary hypertension are recognized clinical manifestations of Antiphospholipid Syndrome (APS).*

***Anti phospholipid syndrome has also not been listed as a cause for Pancytopenia**. Antiphospholipid syndrome may lead to thromboytopenia in (40- 50% cases) and hemolytic anemias in 14-25% of cases but leucopenia has not been mentioned in association with Anti phospholipid syndrome.*

***Pancytopenia is the single best answer of exclusion.***

**Antiphospholipid syndrome (APS)**

- Defined by a clinical association of antiphospholipid antibodies and Hypercoagulability
- Considered a systemic autoimmune disease which is charachterized by recurrent thrombosis or pregnancy complications, along with the presence of Antiphospholipid antibodies.

Primary APS : No cause is identified | Secondary APS : Defined cause like SLE is identified

**Important Clinical Features**

Vascular Thrombosis

- *Recurrent arterial or venous thrombosis* in any tissue or organ is the *most common presentation*

*Pregnancy morbidity*

- *Recurrent spontaneous Abortions*[Q]
- *Pregnancy induced Hypertension*[Q] *(Preeclampsia and ecelampsia)*
- *Placental Insufficiency/Abruption*[Q]
- *Intrauterine Growth Retardation*[Q]

**Important Laboratory Features**

- *Elevated Anticardiolipin antibodies* [Q] *(IgG or IgM)* [Q]
- *Elevated Anti β -2 glycoprotein-1 Antibody* [Q]
- *Presence of Lupus Anticogulant (LA) in plasma* [Q]
- *Thrombocytopenia* [Q]
- *Haemolytic anemia* [Q] *(Coomb's positive)*

***Venous thrombosis***
(More common)

- *DVT is the most*[Q] *common manifestation*
- *Pulmonary Embolism*[Q]
- Pulmonary hypertension from thromboembolic disease

Arterial thrombosis
(less common)

| CNS | Heart | Lungs | Kidney | Bones | Others |
|---|---|---|---|---|---|
| *Stroke*[Q] (Cerebral vessel occlusion) | *Myocardial infarction*[Q] (coronary occlusion) | *Pulmonary Hypertension*[Q] (Pulmonary artery occlusion) | Glomerular Thrombosis *Renal Artery thrombosis*[Q] | *Avascular*[Q] *Necrosis* | |

Evan's Syndrome refers to the clinical association of Autoimmune Thrombocytopenia and Autoimmune Hemolytic anemia. Evan's Syndrome has been reported in 10 percent of patients with Antiphospholipid syndrome

**431. Answer is A (Bleeding disorders):** Harrison 18th/p 987, 2734 *API Textbook of Medicine 8th/ed 306, 307; Harrison's 17th/ 732, 1579, 2082; 'Current Diagnosis and Treatment in Rheumatology' 2nd/219*

***Antiphospholipid Antibody Syndrome is associated with thrombotic disorders and not bleeding disorders.***

*Antiphospholipid Antibody syndrome (APLA) is primarily a disorder of coagulation resulting in a hypercoagulation state.* ***Manifestations of Antiphospholipid Antibody syndrome including recurrent thrombosis and fetal loss result from the hypercoagulable state. Bleeding disorders are not seen.***

**432. Answer is A (Single titre of Anticardiolipin is diagnostic):** Harrison 18th/p 987, 2734 *API Textbook of Medicine 8th/ed 306, 307; Harrison's 17th/ 732, 1579, 2082; 'Current Diagnosis and Treatment 'Rheumatology' 2nd/219*

***Single titre of anticardiolipin antibodies does not establish a diagnosis of APLAb syndrome***
***Laboratory criteria require anticardiolipin antibodies to be present on 2 or more occasions at least 12 weeks apart.***
***A Definite diagnosis of Antiphospholipid Syndrome requires at least one clinical criteria and one laboratory criteria to be met.***

**Diagnostic Criteria for Antiphospholipid Syndrome**

***Definitive Antiphospholipid Syndrome is said to be present if atleast one of the clinical criteria and one of the laboratory criteria are met***

| Clinical Criteria | Laboratory Criteria |
|---|---|
| • **Vascular Thrombosis (Arterial and/or Venous)**<br>One or more clinical episodes of arterial, venous or small vessel thrombosis in any tissue or organ.<br><br>• **Pregnancy morbidity**<br>a. *One or more unexplained deaths* of a morphologically normal fetus at or *beyond the 10th week of gestation*, with normal fetal morpholoogy<br>b. *One or more premature births* of a morphologically normal neonate *before the 34th week of gestation* because of:<br>(a) eclampsia or severe preeclampsia<br>(b) placental insufficiency<br>c. *Three or more unexplained consecutive spontaneous abortions before the 10th week of gestation*, with maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes excluded. | • **Anticardiolipin Antibody** of IgG and /or IgM isotype in serum or plasma *on 2 or more occasions, at least 12 weeks apart*<br>• **Lupus anticoagulant** present in plasma, *on 2 or more occasions at least 12 weeks apart*<br>• **Anti-$\beta_2$- glycoprotein-1 antibody** of IgG and or IgM isotype in serum or plasma, present *on 2 or more occasions, at least 12 weeks apart* |

**Recurrent fetal loss is a common manifestation of Antiphospholipid Syndrome**

*Recurrent fetal loss is an established Pregnancy associated morbidity of Antiphospholipid syndrome and is included in the diagnostic criteria (Refer previous question)*

**Antiphospholipid Syndrome may cause Pulmonary Hypertension**

*Pulmonary hypertension may be seen as a consequence of recurrent subclinical pulmonary emboli (Refer previous question)*

**Warfarin is used in the treatment of Antiphospholipid Syndrome**

*'The mainstay of treatment of Antiphospholipid Syndrome is Warfarin' - Harrison*

**433. Ans is C (Thrombocytosis):** *Dutta 5th 1364: 4th/364*

*Antiphospholipid syndrome is associated with thrombocytopenia and not thrombocytosis.*

| **Common obstetric complications associated with antiphospholipid syndrome are:** |
|---|
| 1. Recurrent fetal loss$^{Q}$ |
| 2. IUGR$^{Q}$ |
| 3. Pregnancy associated hypertension$^{Q}$ |
| 4. Placental abruption$^{Q}$ |
| 5. Recurrent thrombotic events$^{Q}$ |
| 6. Thrombocytopenia$^{Q}$ (and not thrombocytosis). |

**434. Answer is D (Thrombocytosis): Refer Review Notes on Antiphospholipid Syndrome**

***Antiphospholipid Antibody Syndrome is associated with thrombocytopenia and not thrombocytosis.*** *The presence of thrombocytopenia does not appear to reduce thrombotic risk in patients with APS.*

*Recurrent arterial or venous thrombosis in any tissue or organ is the most common presentation. Coomb's Positive Hemolytic Anemia may be seen in up-to 10 percent of patients with Antiphospholipid Syndrome.*

**435. Answer is A (Thrombocytosis):** *Refer previous question*

*Antiphospholipid syndrome secondary to lupus anticoagulant is associated with thrombocytopenia and not thrombocytosis*

**436. Answer is D or none(Increased PT or none):** *CMDT 2008/469; Thrombosis and Hemorrhage' 3rd/326; CMDT 2009/735*

***The Lupus Anticoagulant typically causes an isolated prolongation of APTT. Prothrombin time is usually normal although slight prolongation in PT may also be observed***

*Lupus anticoagulant should be suspected in cases of markedly prolonged PTT without clinical bleeding and normal or slightly elevated PT-* CMDT

Lupus Anticoagulant

- Lupus anticoagulant is an 'antiphospholipid' seen in about 5 to 10% of cases of SLE
- The term 'anticoagulant' is a misnomer as LA acts as a procoagulant casuing increased tendency of thrombosis and does not act as an anticoagulant.

> *'It is mistermed as an 'anticoagulant' because it causes prolongation of PTT in the vitro PTT assay' (This prolongation is produced because lupus anticoagulant being an antiphospholipid binds to the phospholipid used in vitro PTT assays)*
> *PT is usually not affected by the lupus anticoagulant.*

- Lupus anticoagulant is a cause for antiphospholipid syndrome and may present with recurrent thrombosis and pregnancy related morbidity including Recurrent abortions.
- Being an antiphospholipid, presence of lupus anticoagulant cause a false positive VDRL test for syphilis

**Lupus Anticoagulant**
Antiphospholipid seen in 5-10% of cases of SLE

**Clinical presentation**
Presents as
Antiphospholipid syndrome

| Recurrent thrombosis | Pregnancy morbidity |
|---|---|
| • Arterial | • Recurrent obortions |
| • Venous | • IUGR |
| • Vasculopathy | • Pregnancy associated hypertension |
| | • Placental abruption |

**Laboratory features**
- Prolonged PTT
  *Isolated prolongation of PTT with normal (or slightly elevated PT is characteristic of Lupus Anticoagulant*
- False positive VDRL
- Thrombocytopenia may be associated as part of the Antiphospholipid syndrome due to consumption of platlets from recurrent thrombosis and the presence of antiphospholipid autoantibodies directed against the platelets

**437. Answer is D (Thrombotic spells can be followed by severe life threatening haemmorrhage):** *William's Hematology 7th/1763; Current Rheumatology 2nd/218; Samter's Immunologic Disease 6th/573*

***Bleeding episodes after Thrombotic spells may occur as a result of consumptive Thrombocytopenia. However such bleeding episodes are rare even with severe thrombocytopenia and do not lead to life threatening haemorrhage. Catastrophic Life threatening Antiphospholipid Syndrome results from rapid onset thrombosis and ischemia in multiple organ systems and not from severe bleeding.***

**Bleeding is rarely associated with Lupus Anticoagulant**
Lupus Anticoagulant may cause thrombocytopenia, but bleeding complications secondary to thrombocytopenia are rare & severe life threatening bleeding due to Lupus anticoagulant has not been reported in any standard text book.

*'Although Thrombocytopenia is a common finding in patients with APS, bleeding complications are rare, even with severe thrombocytopenia Bleeding in an APS patient should trigger evaluation for the presence of antiprothrombin antibodies and other disorders that may affect hemostasis, such as DIC & Uremia' - William's Hematology*

*'Bleeding is unsual in APS despite the prolongation of in vitro clotting time. When bleeding is present it suggests the presence of antiprothrombin antibody with hypoprothrombinemia but it may rarely be caused by thrombocytopenia'.*
*- Samter's Immunologic diseases*

**438. Answer is C or None (Increased PT or None):** *Harrison 18th/p 1385; Harrison 15th/685; 16th/982, 685; Harrison 17th/1043*

*Prothrombin time is usually not affected by Lupus Anticoagulant.*

- ***The Lupus Anticoagulant typically causes an isolated prolongation of APTT. Prothrombin time is usually normal although slight prolongation in PT may also be observed***
  *'Lupus anticoagulant should be suspected in cases of markedly prolonged PTT without clinical bleeding and normal or slightly elevated PT'- CMDT*
- The presence of LA activity may predispose patients to **venous and arterial thromboembolism** and may cause mid trimester **abortions** – Harrisons 16th/685
- VDRL tests for syphillis are non specific tests, detecting anticardiolipin antibodies.
  Lupus anticoagulants are family of antiphospholipid antibodies of the same class and ***may give a false positive VDRL.***

**Causes of false positive VDRL reactions:**

| Acute false positive (< 6 months) | Chronic false positive (≥ 6 months) |
|---|---|
| • Recent viral infection / immunization | • Aging |
| • Genital herpes | • Autoimmune disorders |
| • Human immunodeficiency virus | • SLE |
| • Malaria | • RA |
| • Parentral drug use | • Parentral drug use. |

**439. Answer is B (Aspirin + Low molecular weight Heparin):** *Harrison's 17th/ 2082; Speroff's Clinical Gynaecological endocrinology & Infertility 7th/1083, 1084*

***The recommended treatment for women with recurrent pregnancy loss associated with antiphospholipid syndrome includes combined Aspirin and Heparin therapy.***

*'In pregnant SLE patients with Antiphospholipid antibodies and prior fetal loss, treatment with heparin (standard or low –molecular- weight) plus low dose aspirin has been shown in prospective controlled trials to increase significantly the proportion of live births'. – Harrison's 17th/2082*

*'Combined aspirin and heparin therapy has proven effectiveness and is the preferred treatment for women with recurrent pregnancy loss associated with antiphospholipid syndrome' - Speroff 7th/1084*

**Antiphospholipid syndrome in pregnancy**

- The risk of pregnancy loss in women with APS and prior pregnancy loss may exceed 60%
- History of recurrent fetal loss in a pregnant woman with Antiphospholipid antibodies is an indication of treatment during pregnancy as these are identifiable and treatable immunologic disorders
- **Treatment options** include Antiplatelet agents such as Aspirin, Anticoagulants such as Heparin / LMWH, and corticosteroids
  ***Aspirin along with Heparin / LMWH*** *is the recommended treatment of choice.*
  *Corticosteroids should be avoided if possible.* If required to control maternal SLE, these should be used at the lowest effective doses for the shortest time required.

## Hemolytic Uremic Syndrome

**440. Answer is D (Positive Coomb's test) :** *CMDT 2001 / 544; CMDT 2003/508; Harrison 16th/679; 15th/750, 690*

*Coomb's test is characteristically negative in patients with HUS.*

*Hemolytic Uremic Syndrome is characterised by a microangiopathic hemolytic anemia, and thrombocytopenia. The LDH is usually elevated out of proportion to degree of hemolysis, and the coomb's test is negative.*

*Coagulation test are normal with the exception of elevated fibrin degradation products* Q ***(explains hypofibrinogenemia)*** *- normal coagulation results exclude DIC.* Q

**Remember the following essentials of diagnosis :**

1. *Microangiopathic hemolytic anemia* Q *(coomb's negative).* Q
2. ***Thrombocytopenia*** Q
3. ***Renal failure*** Q
4. *Elevated LDH* Q
5. ***Normal coagulation tests (exclude DIC)*** Q ***(an exception is elevated FDP)*** Q

**441. Answer is A or None (Hyperkalemia or None) :** *Harrison 14th/959; Harrison 15th/745, 977*

*Hyperkalemia is the single best answer of exclusion.*

HUS may occur with Shigella Dysentriae type I.

**Clinical features in HUS due to shigella as mentioned in *(Harrison 14th/959)* include :**

- Oliguria progressing to anuria and *renal failure*Q
- Drop in hematocrit progressing to severe *anemia and CHF* Q
- ***CNS abnormalities include - encephalopathic symptoms***
  ***- seizures***
  ***- altered consciousness***
  ***- bizzare posturing***
- Laboratory : - Profound *hyponatremia* Q and severe *hypoglycemia* Q may be seen
  - Leukamoid reactions with *increased leucocyte counts* Q may be seen
  - *Thrombocytopenia*Q is common

*Although one might argue that hyperkalemia may as well be a feature of HUS on account of renal failure, I have excluded it because all other options have been mentioned directly in the standard Harrison text.*

## Budd Chiari Syndrome

**442. Answer is C (Paroxymal nocturnal hemoglobinuria):** *Harrison 16th/1862; Robbins 547*

*PNH is the most common cause of Budd Chirai syndrome amongst the options provided.*

- ***Most common cause of Budd chiari syndrome is - thrombosis of hepatic vein***Q
  This is seen in the setting of : - *polycythemia rubra vera* Q
  - *myeloproliferative syndrome* Q
  - ***Paroxysmal nocturnal hemoglobinuria*** Q
  - Oral contraceptive use
  - Hyercoagulable states
- ***It may also result from obstruction of venacava.*** Q
  This may be seen in the setting of :
  - invasion of IVC by tumor such as hepatocellular carcinoma.
  - Idiopathetic membranous obstruction of IVC is the most common cause of this syndrome in Japan.

**443. Answer is D (Thrombosis of hepatic veins):** *Harrisons 17th/1950; Harrisons 16th/1862*

*The most common cause of Budd Chiari syndrome is thrombosis of hepatic veins – Harrisons*

**444. Answer is C (Hepatic vein):** Harrison 18th/p 2561 *Harrison's 16th/1863; 15th/1759: See previous question*

***Budd chiari syndrome is characterized by post sinusoidal obstruction outside the liver at the level of hepatic veins.***
*– Harrison's 15th/1759*

**445. Answer is D (Polycythemia vera):** *Harrisons 17th/267.268; Harrisons 16th/1862; Robbins Pathology Illustrated 6th/883*

***Polycythemia vera is the most common cause for Budd chirai syndrome amongst the options provided.***

## Blood Transfusion

**446. Answer is A (4 hours):** *Wintrobe's Clinical Hematology 13th/565; Blood: Principles and Practice of Hematology; Transfusion Medicine (John Wiley and Sons) 3rd/*

*Blood transfusion should be completed in less than 4 hours because of the dangers of bacterial proliferation, which may occur as blood warms to room temperature.*

*'One unit of red cells is often given in 1 to 4 hours. Infusion of a unit for longer than 4 hours is not recommended, as there is a risk of bacterial proliferation because the opened unit is at room temperature' - Wintrobe's*

**447. Answer is C (35days):** *Wintrobe's Hematology 11th ed. 1657-58; Textbook of Blood Banking and Transfusion Medicine*

*FDA Approved shelf life of blood stored in CPD-A (CPDA-1) Buffer is 35 days (CPD-A or CPDA1 Buffer refers to Citrate-Phosphate-Dextrose buffer supplemented with Adenine and is now one of the standard anticoagulant-preservative solutions in clinical use).*

| *Buffer* | *Shelf Life* |
|---|---|
| *ACD Buffer (Acid Citrate Dextrose Buffer)* | *21 days* |
| *CPD Buffer (Citrate-Phosphate-Dextrose)* | *21 days* |
| *CP2D Buffer (Citrate-Phosphate-Dextrose with 2 times the Dextrose of CPD)* | *21 days* |
| *CPD-A (CPDA-1) Buffer (Citrate-Phosphate-Dextrose with Adenine* | *35 days* |

*Shelf life of stored blood is also known as the expiration date or outdate and is determined by $CR^{51}$ Survival studies which measure how many RBC's stored in preservative solution survive in the circulation 24 hours after transfusion. A minimum of 70 percent stored RBC'S must survive in the first 24 hours.*

**448. Answer is A (Complement mediated Hemolysis is seen):** *Refer text below*

*Acute Hemolytic Transfusion reactions following Blood transfusion are Type II hypersensitivity reactions caused most often by complement mediated hemolysis. These reactions are often life threatening and complications include Oliguria and acute renal failure (decreased renal blood flow).*
*Treatment involves immediate termination of transfusion.*

**449. Answer is A and B (Antigen 'D' determines Rh positivity and Febrile reaction is due to HLA antibodies):** *Harrison 18th/p 953, 955 Ananthanarayan 7th/186, 187; Harrison 17th/711, 710*

*Rh positive or nregative depends on the presence or absence of antigen D (Rh D) on red cells.- Ananthanarayanan* ***Febrile (non hemolytic) transfusion reactions are caused by antibodies directed against donor leukocytes and HLA antigen may mediate these reactions*** *– Harrison 17th/711*

**Anti-D is not a naturally occurring Antibody**
*'There are no natural anti – Rh (anti - D) antibodies in the serum' – Ananthanarayanan*

**Cryoprecipitate does not contain all coagulation factors**
*Cryoprecipitate is a source for fibrinogen, factor VIII and Von-Willebrand factor (VWF) – Harrison 17th/710*

**450. Answer is A (Febrile Non Hemolytic Reaction) :** Harrison 18th/p 953 *Harrisons 17th/711, Harrisons 16th/665*

*The most frequent reactions associated with the transfusion of cellular blood components is a Febrile Non Hemolytic Transfusion Reaction (F N H T R).*

*Febrile Non Hemolytic Transfusion Reactions (F N H T R)*

| Etiology | Clinical presentation | Prevention and Treatment |
|---|---|---|
| • *These reactions are most commonly caused by* antibodies directed against donor leukocytes and HLA antigens[Q]<br>• *These may also be caused by cytokines released from cells within stored blood*<br>• *Patients at risk include*[Q]<br>Multiply transfused patients[Q]<br>Multiparous women[Q] | • *These reaction are characterized by chills and rigors and ≥ 1°C rise in temperature*<br>• *Diagnosis is usually made by excluding other causes of fever in a transfused patient* | • *Most reactions are mild and do not require any further investigations or treatment*<br>• *Their incidence and severity may be reduced by:*<br>- *Use of leucocyte reduced blood products*<br>- *Premedication with acetaminophen or other antipyretic agents* |

**451. Answer is B (Dengue Virus):** *Harrison's 16th/666*

*Dengue virus has not been mentioned as an infectous viral complication of blood transfusion.*

**Viruses associated with blood transfusion:**

***Hepatitis C virus***
***Hepatitis G virus***
***Hepatitis B Virus***
***HIV Type I***
***HTLV Type I***
***Cytomegalovirus*** [Q]
***Parvovirus B-19*** [Q]
***West Nile Virus***
***Human Herpes Virus (HHV)*** [Q]

***Hepatitis C virus :*** *Most common cause of transfusion associated viral hepatitis* [Q]
***Hepatitis G virus :*** *Is a blood borne agent whose modes of transmission have not been defined adequately but tend to parallel those of HCV infection.* [Q]

**452. Answer is None or C (None >> EBV):** Harrison 18th/p 954, 956, 957 *Ananthnarayanan 8th/475; 'Microbiology in Blood Transfusion' by Barbara 1st/211, Harrison's 17th/710, 711, 712*

*Parvovirus B-19, Hepatitis G, Cytomegalovirus and Epstein Bar virus may all be transmitted by blood transfusion.* ***Transfusion transmitted EBV is however a rare event and may hence be selected as the single best answer by exclusion.***

**EBV and Blood Transfusion (Morbidity following EBV Transfusion is Rare)**

*'EBV infection may also follow blood transfusion or marrow transfusion but these are rare* events'– *Ananthanarayan 8th/131*

*'Although transfusion associated EBV is rare, it is nevertheless well documented'- Microbiology in Blood Transfusion 1st/211*

**453. Answer is D (Metabolic Acidosis) :** *'Handbook of Transfusion Medicine' by Hillyer (2001)/194*

***Massive blood transfusion is usually associated with metabolic alkalosis rather than metabolic acidosis***
*Hyperkalemia, Citrate toxicity and Hypothermia are established complications of massive blood transfusion*

**Metabolic acidosis / Alkalosis after Massive Blood Transfusion**

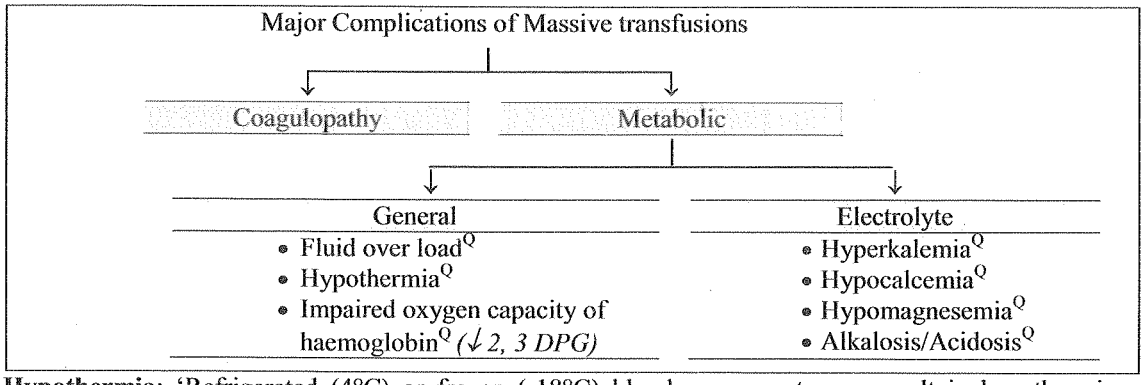
*Banked / stored blood is acidic because of accumulated red cell metabolites. However the actual acid load to the patient is minimal. The acid load on massive blood transfusion is quickly countered by the effect of citrate infusion as citrate is normally metabolized to sodium bicarbonate. It is therefore more common for massively transfused patients to exhibit metabolic alkalosis rather than metabolic acidosis.*

Patients with massive transfusion may present with initial metabolic acidosis, however metabolic alkalosis is more frequent once citrate is metabolized in liver to bicarbonate.

**454. Answer is A (Hypokalemia):** *Harrison's 16th/666; Transfusion Practices by American College of Anaesthetics 3rd/20, 21*

***Massive transfusions are associated with risk of hyperkalemia and not hypokalemia.***

**Massive transfusions: Defined as acute replacement of more than one blood volume within several hours.**




**Hypothermia**: 'Refrigerated (4°C) or frozen (-18°C) blood components can result in hypothermia when rapidly infused' – *Harrison*

**Hyperkalemia, Hypocalcemia & Hypomagnesemia**: *Transfusion Practices by American College of Anaesthetics 3rd/20, 21*

***The potential metabolic problems resulting from blood transfusion are hyperkalemia, hypocalcemia and hypomagnesemia'*** – *Transfusion Practice – American society of Anesthesiologists 3rd/20, 21*

- **Hyperkalemia:**
  Potassium increases in the plasma of stored blood as potassium leaves viable erythrocytes.
  However, hyperkalemia is rarely a problem in adults for two reasons:
  - there is very little plasma in Red Blood Cells and
  - the potassium that is present leaves the intravascular space of the recipient and rapidly moves intracellularly.

  Neonates and patients in renal failure are at increased risk of hypokalemia.
- **Hypocalcemia:**
  Citrate present in anticoagulant preservative solutions chelates calcium and causes hypocalcemia
- **Hypomagnesemia:**
  Citrate also has an affinity for the magnesium ion and the occurrence of hypomagnesemia in the setting of massive transfusion has been reported.
- **Alkalosis/Acidosis**
  Stored blood is acidic (pH of 6.6 to 6.9) due to citric acid in the antocoagulant and the accumulation of carbondioxide and lactic acid from erythrocyte metabolism.

| **Metabolic acidosis / Alkalosis after Massive Blood Transfusion** |
|---|
| Banked / stored blood is acidic because of accumulated red cell metabolites. However the actual acid load to the patient is minimal. The acid load on massive blood transfusion is quickly countered by the effect of citrate infusion as citrate is normally metabolized to sodium bicarbonate. ***It is therefore more common for massively transfused patients to exhibit metabolic alkalosis rather than metabolic acidosis.*** |
| *Patients with massive transfusion may present with initial metabolic acidosis, however metabolic alkalosis is more frequent once citrate is metabolized in liver to bicarbonate.* |

- **Citrate Toxicity:**
  Citrate toxicity occurs when ionized calcium is significantly reduced by citrate present in anticoagulant preservative solutions and thereby inhibits the coagulant cascade.

**455. Answer is B (Direct Coomb's test):** *Harrison 18th/p 954 ; 17th/710; 'Clinical Hematology & Oncology' (Churchill Livingstone) 2003/433*

***A direct Coomb's test or direct antiglobulin test (DAT) on post-transfusion blood sample from patient should be done to detect antibodies directed against the transfused red blood cells***

*A positive direct antiglobulin test (positive direct Coomb's test) that develops during a red blood cell transfusion or immediately following a transfusion strongly suggests that the patient has an antibody directed against the transfused red cells. This is consistent with a hemolytic transfusion reaction.*

**Blood bank related action for every suspected case of mismatched blood transfusion**

- Every suspected case of mismatched blood transfusion *should be reported* to the blood bank.
- A correctly labeled post transfusion blood sample and any untransfused blood should be sent back to the blood bank for analysis.
- ***At the blood bank the post transfusion specimen should be tested for evidence of hemolysis*** *(serum haptaglobin, LDH, hemoglobin and bilirubin)* **and** ***a direct antiglobulin test (direct Coomb's test) should be performed***.
  *A positive direct Coomb's test confirms the presence of antibodies / complement directed against the transfused RBCs and confirms a hemolytic transfusion reaction.*

**456. Answer is E (All of the above):** Harrison 18th/p 952, 953 *Refet text below; Harrison 17th/709, 710*

**Commonly used blood components**

| Product | Description | Common Indications |
|---|---|---|
| **Whole Blood**<br>*1 unit = 450 ml ± 45ml* | No elements removed<br>Contains RBC, WBC, plasma and platelets (WBC & platelets may be nonfunctional)<br>Deficienct in factors V & VII | • Not for routine use<br>• Acute, massive bleeding<br>• Open heart surgery<br>• Neonatal total exchange |
| **Packed Red Cells (PRBC)**<br>*1 unit = 250 – 300 ml* | Most plasma, WBC, platelets removed;<br>1 unit should raise HCT 3% | • Replacement in chronic and acute blood loss, GI bleeding, trauma |
| **Leukocyte -Poor Red cells (Leukocute reduced) Red cells**<br>*1 unit = 200-250 ml* | Most WBC removed by filtration to make it less antigenic<br>$< 5 \times 10^6$ WBC, few platelets, minimal plasma | • Potential renal transplant patients<br>• Previous febrile transfusion reactions<br>• Patients requiring multiple transfusions (leukemia etc) |
| **Washed RBCs**<br>*1 unit = 300 ml* | Like leukocyte-poor red cells, but WBC almost completely removed<br>$< 5 \times 10^6$ WBC, no plasma | • As for leucocyte poor red cells, but very expensive and much more purified. |
| **Granulocytes, Phoresis**<br>*1 unit = 220 ml* | Some RBC, $> 1 \times 10^{10}$ PMN/unit, Lymphocytes, platelets | |
| **Platelets (smple unit)**<br>*1 pack = about 50 ml* | 1 "pack" should raise count by 5000-8000<br>"6 pack" means a pool of platelets from 6 units of blood.<br>$> 5 \times 10^{10}$ platelets unit, contains RBC, WBC | • Decreased production or destruction (aplastic anemia, acute leukemia, post-chemo etc)<br>• Counts <5000-10,000 (risk of spontaneous hemorrhage)<br>• Counts 10,000-30,000 if risk of bleeding (headache, GI losses, contagious petechiae) or active bleeding<br>• Counts <50,000 for major surgery<br>• Usually not indicated in ITP or TTP unless life-threatening bleeding or preoperative status. |
| **Platelets (Phoresis unit)**<br>*1 unit = 300 ml* | $> 3 \times 10^{10}$ platelets/unit | May be HLA matched |
| **Leukocyte- Reduced Platelets** | As above, but $< 5 \times 10^6$ WBC/unit | • May decrease febrile reaction and CMV transmission, alloimmunization to HLA antigens |
| **Cryoprecipitate ("Cryo")**<br>*1 unit = 10 ml* | Contains factors VIII, XIII, von Willebrand factor and fibrinogen | • Hemophilia A (factor VIII deficiency), when safer factor VIII concentrate not available;<br>• von Willebrand disease, fibrinogen deficiency |
| **Fresh frozen Plasma (FFP)**<br>*1 unit* =150-250 ml<br>(400-600 ml if single-donor pheresis) | Contains factors II, VII, IX, X, XI, XII, XIII and heat labile V and VII<br>About 1 h to thaw | • Emergency reversal of warfarin<br>• Massive transfusion (>5 L in adults)<br>• Hypoglobulinemia (IV immune globulin preferred)<br>• Suspected or documented coagulopathy (congenital or acquired) with active bleeding or before surgery<br>• Clotting factor replacement when concentrates unavailable<br>• Not recommended for volume replacement |

**457. Answer is D (4 hours)**: *Wintrobe's Clinical Hematology 13th/565*;

***Once the blood bag is opened by puncturing one of the sealed ports, the platelets must be administered within 4 hours.***

**458. Answer is A (5 days):** *Wintrobe's Hematology 11th ed. 1681*

***Platelets are approved by FDA for storage up to 5 days at 20-24 (Room Temperature) because of risk of bacterial contamination.***

*The FDA has proposed two criteria by which the shelf life of platelets may be extended up to 7 days. First, products must be stored in containers approved for 7-day storage (these are available). Second, products must test negative for bacteria with an FDA-approved release test.*

**459. Answer is C (4 days):** *Wintrobe's 13th/ 552*

*In healthy adults the half life of transfused platelets is 3 to 5 days (Average 4 days).*

**460. Answer is D (+ 20-24 degrees Celsius):** *Wintrobe's 13th/ 552*

***FDA approves platelets for storage at 20-24 (Room Temperature) for up to 5 days with continuous gentle agitation.***

**461. Answer is A (Platelets carry the Rh antigen):** *Wintrobbe Hematology 13th/569*

*Platelets do not carry the Rh Antigen.*

Platelet transfusion and Incompatibility

- Platelets bear both intrinsic and adsorbed antigens of the ABH system. The clinical importance of ABO compatibility in platelt transfusion is contoversial. Transfusion of ABO incompatible platelets may be associated with decreased posttransfusion platelet recovery and normal survival.
- Platelets do not carry the Rh antigen but the donors RH type is important because the red cells present in the platelet concentrate may immunizeRH negative recepients.
- Platelet products contain a significant amount of donor plasma

**462. Answer is B (Factor IX):** *Harrisons 16th/664*

*Cryoprecipitate is not a source for factor IX.*

| Cryoprecipitate is a source for |
|---|
| *Fibrinogen*$^{Q}$ |
| *Factor VIII*$^{Q}$ |
| *VWF*$^{Q}$ |

Cryoprecipitate also contains factor XIII (I), and fibroructin

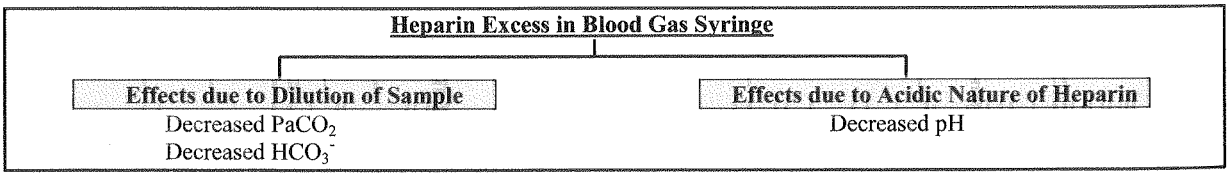
- Cryoprecipitate is ideal for supplying fibrinogen to the volume deficient patient
- Cryoprecipitate is indicated for factor VIII deficiency (Hemophilia A) when fresh Frozen plasma is not available
- Cryoprecipitate may also supply VWF to patients will dysfunctional (type II) or absent (type III) von Willebrand disease

**463. Answer is D (All of the above):** *Clinical Laboratory Medicine 6th/396; Pulomary Respiratory Therapy Secrets 2nd (2001)/27*

*Dilution of a sample with heparin can cause erroneously low value for pH, $pCO_2$ and $HCO_3^-$.*

Heparin and Blood Gas Measurements

- Heparin is the preferred anticoagulant for blood gas specimens
- Heparin is used in blood gas syringes to avoid coagulation of the blood sample, as clots interfere with the function of the blood gas analyzer. Heparinization of blood sample also limits the deposition of proteins on the electrodes.
- ***However excess heparin can affect blood gas analysis by lowering the PaCO2 and calulcated HCO3- by dilutional effect and the pH as heparin is acidic.***




## Miscellaneous

**464. Answer is D (14 g/dl):** *Wintrobe's Clinical Hematology 13th/588*

***The lower limit of normal Hemoglobin concentration at birth is 14g/dl***

**Hemoglobin Values in Infants and Children**

***The lower limit of normal Hb concentration at birth is 14g/dl, and this decreases to 11 g/dl by 1 year of age***. This Hb decrement, referred to as *the physiologic anemia of infancy,* occurs as part of the normal physiologic adaptation from the relatively hypoxia intrauterine existence to the well-oxygenated extra-uterine environment.

**465. Answer is B (<11 g/dl):** WHO Statement

***Anaemia in an infant aged 9 months is defined as a Hb value less than 11 g/100ml of venous blood***

**WHO Defination of Anemia**

According to WHO 'anemia' should be considered to exist in those whose haemoglobin levels ***are lower than the figures given below***

| Age Group | Hb values (g/100 ml of venous blood of persons at sea level) |
|---|---|
| Children aged 6 months to 6 years | *11* |
| Children aged 6-14 years | *12* |
| Adult males | *13* |
| Adult females, nonpregnant | *12* |
| Adult females, pregnant | *11* |

**466. Answer is B (<12g/dl):** *WHO Statement: Refer table in previous question*

***Anaemia in a child aged 12 years can be defined as Hb value less than 12 g/100ml of venous blood***

**467. Answer is A (Methaemoglobinemia):** *Harrison 18th /857,858*

***Pronounced cyanosis together with chocolate brown colour of freshly drawn blood suggests a diagnosis of methaemoglobinemia.***

**Methaemoglobinemia**

- Methaemoglobinemia is an uncommon but distinct cause of central cyanosis in the absence of hypoxemia or cardio vascular compromise
- Methaemoglobinemia occurs when a significant concentration of hemoglobin (Hb) is oxidized to methaemoglobin (Met Hb)

  *When the haem moety (iron atoms) of Hb molecule encounter a strong oxidizing agent iron loses an electron and switches from the Ferrous ($2^+$) to Ferric ($3^+$) state turning Hb to 'Met Hb'*
- Methaemoglobin has such high oxygen affinity that virtually no oxygen is delivered

**Presentation**

- Methaemoglobinemia most commonly presents as *cyanosis unresponsive to supplemental oxygen*

  The most notable physical examination finding is generalized cyanosis which can manifest as muddy brown dark mucus membranes before proceding to global skin discolaration
- 'The charachteristic ***muddy appearance (chocolate brown)*** of freshly drawn blood can be a critical clue'

  *- Harrison's 18th/858*

  *Blood appears dark brown, brownish, muddy or chocolate in colour immediately after withdrawal. In contrast to normal venous blood, the color does not change with addition of oxygen or agitation in the air'- *Diffirential diagnosis in Internal Medicine (Thieme) 2007/709*

  *Methaemoglobinemia >15% cause symptoms of cerebral ischaemia*
  *Methaemoglobinemia > 60% is usually lethal*

**Diagnosis**

- *The best diagnostic test for Methaemoglobinomia is 'Methaemoglobin Assay'*

**Treatment**

- The most effective emergency management for methaemaglobinemia is *administration of Methylene blue*$^{Q}$ which serves as an antidote (intravenous)

  *Methylene blue is not effective in patients with methaemoglobinemia due to Hemoglobinopathy M*$^{Q}$ *(Haemoglobin M)*
  Methylene blue is *contraindicated in patients with G6 PD deficiency*$^{Q}$ since it can cause severe hemolysis due to its potential for oxidation

**Outline of The Four Main Pathways to MetHb Production**

1. Congenitally abnormal hemoglobin: Hemoglobin M
   - Hemoglobin M is passed as an autosomal dominant trait affecting either the alpha or beta chain of hemoglobin; homozygous Hb M affecting both alpha and beta chains is incompatible with life.
   - Amino acid substitution (often a tyrosine for histidine) near the heme iron facilitates iron oxidation.
2. Inherited enzyme deficiencies: NADH-dependent cytochrome $b_5$ -reductase and cytochrome $b_5$ deficiency.
   - Deficiency of either cytochrome $b_5$ or its reducing enzyme, cytochrome $b_5$-reductase, decreases reduction of MetHb back to Hb
3. Nitrite ($NO_2$), other oxidants and oxygen-reducing compounds
   - Nitrites are a common oxidizing source of MetHb production.
   - Reducing agents paradoxically produce methemoglobinemia by reducing oxygen to a free radical or water to $H_2O_2$, which then oxidizes hemoglobin.
4. "Sensitive" hemoglobin: Blue baby syndrome
   - Bacteria in the immature gastrointestinal tracts of infants convert nitrate ($NO_3$) to the powerful oxidant nitrite ($NO_2$).
   - Infants have a relative NADH-dependent reductase deficiency (only 50% of adult levels) and are more susceptible to oxidative injury.



**468. Answer is B (Renal failure)**

*Renal Failure is associated with reduced erythropoietin levels due to decreased production of erythropoietin by the diseased kidney.*

*The kidney is the primary site of erythropoietin production producing more than 85 percent of total erythropoietin. Chronic Renal failure is associated with severe anemia. The most important contributor to the anemia of chronic renal failure is insufficient production of Erythropoetin.*

*Patients with inflammatory disorders (Anemia of chronic disease) also have inappropriately low levels of Erythropoetin. Examples include Rheumatoid arthritis, some forms of Cancer and AIDS. This is believed to result from suppression of EPO gene expression by inflammatory cytokines in these disorders.*

**Causes of Anemia in Chronic Renal Failure and other Chronic Diseases**

- *Decreased production of Erythropoetin*[Q]
- *Reduced survival of RBCs*[Q]
- *Impaired flow of iron from bone marrow macrophages to erythroblasts.*

**469. Answer is B (White cell infusion):** Harrison 18th/p 476 *Read text below : Harrison 14th/ 359, 541; Harrison 17th/ 379*

***While all might be used, the best to be eliminated here is a 'white cell transfusion' as its exact role is yet to be established. White cell infusion (transfusion) as a measure is still controversial-*** *Harrison*

- Neutropenic patients are highly susceptible to infections, and therefore, ***surgical cleanliness*** is the first step to ensuring a decreased infection potential - ***Repeated hand washing***
- ***Prophylactic antibiotics*** are certainly required. Patients with luekopenias and leukocyte dysfunction often have delayed inflammatory responses to infection. Therefore clinical manifestations may be minimal despite overwhelming infection. *This necessitates early and prompt institution of prophylactic antibiotics at the earliest suspected sign of infection. Prolonged antibiotics are often required.*
- ***Recombinant G-CSF and M-CSF*** is indicated in the management of certain forms of *neutropenia due to depressed production*. These enhance granulocyte recovery specially that after chemotherapy and consequently shorten the period of maximal vulnerability to fatal infections.
- *Other agents* used include *INF* which non specifically enhance phagocytic cell function and *short courses of Glucocorticoids*.
- ***White cell infusion (transfusion) as a measure is still controversial- Harrison***

*Thus while all might be used, the best to be eliminated here is a 'white cell transfusion' as its exact role is yet to be established, and its role is still controversial.*

**470. Answer is B (Paroxysmal Cold Haemoglobinuria (PCH)):** *Harrisons 18th/882, 883, 895*

***Paroxysmal Cold Hemoglobinuria (PCH) is a benign self-limiting autoimmune hemolytic anemia. PCH does not undergo leukemic transformation and is hence not considered a Preleukemic condition. Recovery is the rule in Paroxysmal Cold Hemoglobinuria.***

**Paroxysmal Nocturnal Haemoglobinuria may be considered a Preleukemic condition**

*'PNH may evolve into Aplastic anemia and PNH may manifest itself in patients who previously have Aplastic Anemia.* ***Rarely (estimated 1-2% of all cases) PNH may terminate in Acute Myeloid Leukemia'.*** *– Harrison 18th/883*

**Myelodysplasia (Myelodysplastic Syndrome) is a Preleukemic condition**

*'Myelodysplastia is a clonal hematopoietic stem cell disorder leading to impaired cell proliferation and differentiation Cytogenetic abnormalities are found in approximately one half of patients and some of the same specific lesions are also seen in frank leukemia.* ***The type and number of cytogenetic abnormalities strongly correlate with the probability of leukemic transformation*** *and survival' – Harrison 18th/895*

**Aplastic Anemia may be considered a Preleukemic condition**

*'Recent studies have shown that long term survivors of acquired aplastic anemia may be at high risk of subsequent malignant diseases or late clonal hematological diseases often years after successful immunosuppressive therapy.* ***One Hypothesis has postulated that aplastic anemia is a Preleukemic condition'.***

*– 'Clinical Hematology' (Lippincott- Williams) 4th/123*

**471. Answer is D (Primary Thrombocytosis):** Harrison 18th/p 470, 903 *Harrison's 17th/374, 676*

***Splenomegaly is least likely to be associated with Primary Thrombocytosis amongst the options provided***

*CML, Polycythemia Vera and Myelofibrosis are characteristically associated with massive splenomegaly.*
*Primary Thrombocytosis is only occasionally associated with mild splenomegaly and hence is the single best answer of choice*

**Primary Thromobcytosis is only occasionally associated with mild splenomegaly**

*'Physical examination is generally unremarkable, except occasionally for mild splenomegaly'-Harrison's 17th/676*

**CML, Polycythemia Vera and Myelofibrosis are associated with massive splenomegaly** - *Harrison's 17th/374*

| **Diseases associated with massive splenomegaly** *(Harrison's 17th/374)* |
|---|
| • ***Chronic myelogenous leukemia*** |
| • *Lymphomas* |
| • *Hairy cell leukemia* |
| • ***Myelofibrosis*** *with myeloid metaplasia* |
| • ***Polycythemia Vera*** |
| • *Gaucher's disease* |
| • *Chronic lymphocytic leukemia* |
| • *Sarcoidosis* |
| • *Autoimmune hemolytic leukemia* |
| • *Diffuse splenic hemangiomatosis* |

**472. Answer is B (Lepirudin):** *Goodman & Gillman's Manual of Pharmacology (2007) 955; 'Clinical Hematology & Oncology' by Furie (2003) /488.*

***Lepirudin (direct thrombin inhibitor) is a recommended agent for Heparin induced thrombocytopenia and thrombosis.***

Currently Recommended Agents for Heparin Induced Thrombocytopenia

- ***Lepirudin*** *(Direct Thrombin Inhibitor)*
- *Argatroban (Direct Thrombin Inhibitor)*
- *Danaparoid (Mixture of Non Heparin Glycosaminoglycans)*

*Bivalirudin (Direct thrombin inhibitor) is under evaluation for HIT*

## Heparin Induced Thrombocytopenia (HIT)

- Heparin Induced Thrombocytopenia is an important complication / adverse effect of Heparin administration that necessitates use of alternative agents to treat or prevent thrombus formation
- HIT is usually seen as a complication of the use of unfractionated heparin but may also be seen with the use of LMWH

  HIT may be non immune mediated (Type I, Mild) or immune mediated due to development of antibodies (Type 2/ Significant)

| Type I | Type II |
|---|---|
| *Non immune mediated* | *Immune mediated* |
| *Benign* | *Severe* |
| *Mild Thrombocytopenia* | *Significant thrombocytopenia* |
| *Heparin Therapy may be continued* | *Heparin must be discontinued immediately* |

- Heparin Induced thrombocytopenia Type II is a serious form of HIT that can result in serious complications
- The diagnosis of Immune mediated HIT depends on clinical criteria with confirmation by specific laboratory tests

| Clinical Criteria for Immune Mediated (Type II) HIT |
|---|
| • Thrombocytopenia < 150, 000/μl or a 50% decrease from pretreatment values |
| • Thrombocytopenia follows heparin exposure by at least 5 days (Time taken to form antibodies) |
| • Reasonable exclusion of other clinical causes of thrombocytopenia |
| • *Onset of new thrombotic event or extension of previous thrombosis* |

- **Management of HIT (Immune mediated)**
- Direct Thrombin Inhibitors

  ***Lepirudin and Argobatran along with Danaparoid are the recommended alternative anticoagulants for patients with Heparin Induced thrombocytopenia.***

  *Direct thrombin inhibitors (Lepirudin and Argobatram) are usually preferred but all three drugs are effective anticoagulants and the choice of drug depends on personal experience and patient characteristics like hepatic or renal insufficiency and desired route of administration*
- Heparin administration *should be stopped immediately.*
- Low Molecular Weight Heparin (LMWH) *should not be substituted* because it may cross react with antI-heparin antibodies
- Warfarin *should not be used* until the thrombocytopenia is resolved and the patient is adequately anticoagulated with another agent. Warfarin may precipitate venous limb gangrene or multicentric skin necrosis in patients with HIT

| Comparison of Danaproid, Lepirudin, and Argatroban for the treatment of Heparin induced Thrombocytopenia | | | |
|---|---|---|---|
| | **Danaproid** | **Lepirudin** | **Aragtroban** |
| Mechanism of action | Primarily inhibits Xa in a complex with Antithrombin III | Directly inhibits thrombin | Directly inhibits thrombin |
| Administration | IV or SC | IV | IV |
| Half-life | 24 hours | 13 hours | 30 minutes |
| Reversible | No | No | No |
| Monitoring | Anti-Xa activity using a danaproid standard | aPTT | aPTT |
| Use in pregnancy | Several reported cases | No reported experience | No reported experience |
| Dose adjustment for renal failure | Yes, monitor Xa activity dosely in patients with renal insufficiency | Yes, monitor Xa activity closely in patients with renal insufficiency | No |
| Special considerations | Cross- reacts with heparin-induced antibodies in some cases | Antibodies may develop to lepirudin and prolong the half –life | |

*All three drugs are anticoagulant in patients with heparin-induced thrombocytopenia. The choice of drug depends on personal experience and patient characteristics such as renal or hepatic insufficiency, desired route of administration.*

# Cardiovascular System

# ESSENTIAL REVISION NOTES

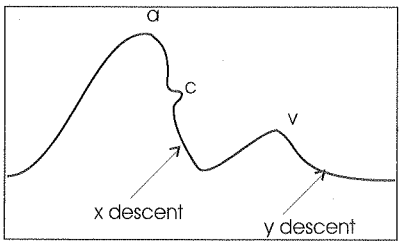
## Arterial and Venous Pulses

### Types of Pulses

| Pulses alternans ♀ | Bisferiens pulse ♀ | Pulsus paradoxus ♀ | Dicrotic pulse ♀ |
|---|---|---|---|
| • Regular alteration of pressure in pulse with regular rhythm (single peak)<br>• Seen in<br>- LVF ♀<br>- May be seen in all conditions leading to LVF | • Two systolic peaks<br>• Seen in<br>- Aortic regurgitation♀ ± AS<br>- Hypertrophic cardiomyopathy ♀ | • Normal decrease in systolic pressure during inspiration is accentuated ♀<br>• Seen in<br>- Pericardial tamponade ♀<br>- S.V.C. obstruction ♀<br>- COPD/Acute Severe Asthma<br>- Constrictive pericarditis<br>- Pulmonary embolism<br>- Hypovolemic shock | • Has two palpable waves are in systole and one in diastole.<br>• Seen in<br>- Dilated cardiomyopathy |

## Jugular Venous Pulse (JVP)

### Jugular venous pulse:




*Various Waveforms in Jugular Venous Pulse*

| | | |
|---|---|---|
| **a waves :** | Due to distention produced by right atrial contraction. | |
| **c waves :** | Are positive waves produced by bulging of tricuspid valve into right atrium during right ventricular isovolumetric contraction. | |
| **v waves:** | Due to increasing volume of blood in the right atrium during ventricular systole when the tricuspid valve is closed. | |
| **a – x descent:** | Due both to atrial relaxation and to the downward displacement of the tricuspid valve during ventricular systole. | |
| | Accentuated in | Reduced with |
| | • ***Constrictive pericardtis***<br>• ***Cardiac temponade***<br>• ***Restrictive*** cardiomyopathy | • ***Right ventricular dilatation***<br>Reversed with<br>• ***Tricuspid Regurgitation*** |
| **v – y descent:** | By the opening of the tricuspid valve and the subsequent rapid inflow of blood into the right ventricle. | |
| | Accentuated in | Reduced with |
| | • ***Tricuspid regurgitation***<br>• ***Constrictive pericarditis*** | • ***Tricuspid stenosis***<br>• ***Right / Atrial Myxoma***<br>***(Suggests obstruction to right ventricular filling)*** |
| **y – a descent:** | Due to continuous diastolic inflow of blood into great veins, right atrium and ventricle, which are all in free communication during diastole. | |

**'a' waves in Jugular Venous Pulse**

| Large 'a' waves : | Cannon 'a' waves : | Absent 'a' waves : |
|---|---|---|
| • ***Tricuspid stenosis*** $^{Q}$<br>• Pulmonary stenosis $^{Q}$<br>• ***Pulmonary hypertension*** $^{Q}$ | • Regularly<br>- During ***junctional rhythm*** $^{Q}$<br>• Irregularly<br>- Atrioventricular dissociation with ventricular tachycardia<br>- *Complete heart block* $^{Q}$ | *Atrial fibrillation* $^{Q}$ |

**Prominent x descent and y descent**

| Feature | Tamponade | Constrictive pericarditis | Restrictive cordiomyopathy | RVMI |
|---|---|---|---|---|
| ***Prominent y descent*** | ***Absent*** | Usually present | Rare | *Rare* |
| ***Prominent x descent*** | Present | Usually present | Present | *Rare* |

## Cardiac Auscultation: Heart Sounds and Murmurs

### Heart Sounds

| Feature | 1st heart sound | 2nd heart sound | 3rd heat sound | 4th heart sound |
|---|---|---|---|---|
| Character | High pitched (lower than $S_2$) Slightly prolonged "lub" | High pitched (higher than $S_1$) Shorter "dup" | Soft low pitched weak rumbling | Low pitched heart sound |
| Duration | 0.14 second | 0.11 sec | 0.1 sec | - |
| Frequency | 25-45 Hz | 50 Hz | - | ***< 20 Hz*** $^{Q}$ |
| Cause | Sudden closure of mitral & tricuspid valves | Closure of aortic & pulmonary valves | ***Rapid ventricular filling*** $^{Q}$ d/t inthrushing of blood from atria | ***Ventricular filling*** $^{Q}$ d/t atrial contraction causing inthrushing of blood |
| Timing | Start of ventricular systole | Just after end of ventricular systole | Begining of middle third of diastole | Immediately before 1st heart sound (presystolic) |
| Heard | Better heard with Diaphram | Better heard with Diaphram | ***Better heard with the Bell*** | ***Better heard with the Bell*** |

***$S_3$ & $S_4$ can often not be heard with a stethoscope (ear)*** $^{Q}$ and require phonocardiogram
$S_3$ often and $S_4$ sometimes can be recorded in phonocardiorgam

*The first and second heart sounds and opening snaps are heard better with the diaphragm, and low-pitched sounds such as the third or fourth heart sound are beter heard with the bell of stethoscope – Hutchisons 20th/ 174*

### First Heart Sound (S1)

Causes of Soft S1

| Poor conductance of sound through chest wall | Decrease in rate of LV pressure development | PR interval and velocity of valve closure | Mobility of valve |
|---|---|---|---|
| • ***Obesity***<br>• *Emphysema*<br>• ***Pleural effusion***<br>• *Pericardial effusion* | • Myxoedema<br>• *Cardiomyopathy*<br>• *Acute MI*<br>• ***Mitral regurgitation*** | • *Prolonged PR interval eg 1st degree heart block* | ***Severe calcification of valve or reduced mobility of valve is associated with soft S1.***<br>*Long standing mitral stenosis is associated with severe calcification of mitral valve and soft S1.* |

## Causes of Loud S1

**Tachycardia**

*S1 is louder if diastole is shortened due to tachycardia*

- Anemia
- Anxiety
- Fever

**Increased / Prolonged AV Flow**

**Increased AV Flow**

| Increased AV Flow due to High Cardiac output | Increased AV flow due to Left to Right shunting |
|---|---|
| • Thyrotoxicosis<br>• AV fistula | • ASD<br>• PDA<br>• Other conditions |

**Prolonged AV Flow**

Because of prolongation of AV flow due to stenosis

- Mitral stenosis
- Tricuspid stenosis

**Short PR interval (Velocity of valve closure)**

At short PR intervals the mitral valve leaflets are maximally separated by atrial contraction. At the onset of LV systole the mitral valve leaflets therefore close with a high velocity and with a large excursion resulting in loud S1.

## Pathological Split $S_1$

| **Normal splitting** (T1 follows M1 after a longer gap : M1 T1) | **Reverse splitting** (T1 precedes M1 : T1 M1) |
|---|---|
| • Right Bundle Branch Block<br>• LV pacing<br>• Ectopic beats and Idioventricular rhythms originating in Left Ventricle<br>• Ebstein's anomaly | • ***Left Bundle Branch Block***<br>• RV pacing<br>• Ectopic beats and Idioventricular rhythms originating in Right ventricle<br>• ***Severe Mitral Stenosis and Atrial Myxoma*** |

# Second Heart Sound (S2)

## Causes of Single S2 (No Splitting)

### Causes of single $S_2$

**Conditions causing Delayed Aortic Closure**

All conditions associated with delayed $A_2$ can produce a single $S_2$ when the splitting interval becomes less than 30ms

Causes of Delayed A2

- Delayed electrical activation of the right ventricle
  - Complete RBBB (proximal type)
  - Left ventricular paced beats
  - Left ventricular ectopic beats
- Prolonged right ventricular mechanical systole
  - Acute massive pulmonary embolus
  - Pulmonary hypertension with right heart failure
  - ***Pulmonic stenosis*** with intact septum (moderate to severe)
- Decreased impedence of the pulmonary vascular bed (increased hangout)
  - Normotensive atrial septal defect
  - Idiopathic dilation of the pulmonary artery
  - ***Pulmonic stenosis*** (mild)
  - Atrial septal defect
  - Unexplained AES in normal subjects

**Conditions in which one component of $S_2$ is either absent or inaudible**

Conditions in which one component of $S_2$ is either absent or in audible will produce a single $S_2$

- ***Severe TOF***
- Severe semilunor valve stenosis
  - severe AS
  - ***severe PS***
- ***Pulmonic valve atresia***
- Tricuspid valve atresia
- Eisseminger syndrome

Semilunar valves include Aortic valve, Pulmonary valve and trancal valves

**Condition resulting in inability to hear the fainter of the two components of the sound (usually $P_2$)**

These conditions also produce a single $S_2$

- Emphysema
- Obesity
- Respiratory noise

**Normal Physiological Splitting** *(Note: Audible splitting during expiration is considered Abnormal)*

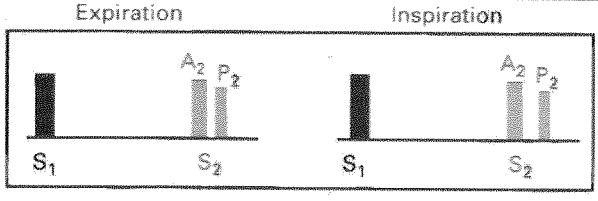
| Normal Physiological Splitting | |
|---|---|
| No audible splitting on Expiration; Audible splitting present on Inspiration. | |
| • During expiration the Aortic sound (A2) and pulmonic sound (P2) are separated by less than 30 ms and are appreciated as a single sound<br>• During inspiration the splitting interval widens and A2 and P2 are clearly separated into two distinctly audible sounds. | Expiration Inspiration<br> <br><br>Audible Expiratory Splitting |

**Abnormal Expiratory Splitting of S2:** *(Note: Audible splitting during expiration is considered Abnormal)*

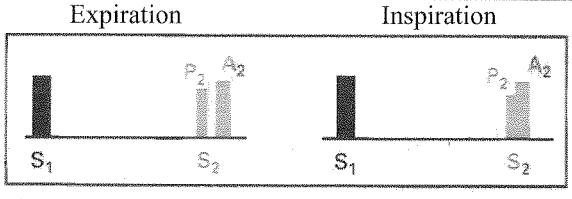
**Abnormal Expiratory Splitting of S2**
***(Audible splitting during expiration is considered Abnormal)***

Audible splitting during both expiration and inspiration

- Wide physiological splitting
- This is caused by delayed P2/early A2




- Reversed Splitting
- This is caused by delayed A2/early P2




*This is associated with Paradoxical movements i.e. P2 moves towards A2 with inspiration and hence splitting interval narrows with inspiration.*

| Wide Physiologic Splitting of the second Heart Sound |
|---|
| **Delayed pulmonic closure** |
| • Delayed electrical activation of the right ventricle<br>- Complete RBBB (proximal type)<br>- Left ventricular paced beats<br>- Left ventricular ectopic beats |
| • Prolonged right ventricular mechanical systole<br>- Acute massive pulmonary embolus<br>- Pulmonary hypertension with right heart failure<br>- Pulmonic stenosis with intact septum (moderate to severe) |
| • Decreased impedence of the pulmonary vascular bed (increased hangout)<br>- Normotensive atrial septal defect<br>- Idiopathic dilation of the pulmonary artery<br>- Pulmonic stenosis (mild)<br>- ***Atrial septal defect***<br>- Unexplained AES in normal subjects |
| **Early aortic closure** |
| • Shortened LVET<br>- ***Mitral regurgitation***<br>- ***Ventricular septal defect*** |

| Reversed Splitting of the second Heart Sound |
|---|
| **Delayed aortic closure** |
| • Delayed electrical activation of the left ventricle<br>- Complete LBBB (proximal type)<br>- Right ventricular paced beat<br>- Right ventricular ectopic beats |
| • Prolonged left ventricular mechanical systole<br>- Complete LBBB (peripheral type)<br>- Left ventricular outflow tract obstruction<br>- Hypertensive cardiovascular disease<br>- Arteriosclerotic heart disease<br>  - Chronic ischemic heart disease<br>  - Angina pectoris |
| • Decreased impedance of the systemic vascular bed (increased hangout)<br>- Poststenotic dilation of the aorta secondary to aortic stenosis or regurgitation<br>- Patent ductus arteriosus |
| **Early pulmonic closure** |
| • Early electrical activation of the right ventricle<br>- Wolff-Parkinson-White syndrome, type B |

**Fixed Wide-Spitting of S2**

| Causes of Fixed (wide) split |
|---|
| • ***ASD (Most characteristic cause for wide fixed splitting)*** |
| • Pulmonic Stenosis |
| • *Acute Right Heart Failure (Pulmonary Embolism)* |

## Third Heart Sound (S3)

- *It is a low frequency sound* Q
- *It is a diastolic heart sound that occurs shortly after S2* Q
- *It occurs during rapid filling of the ventricles (termination of rapid filling)* Q
- *It is best heard at the apex in the left lateral position* Q
- *It is better heard with the bell of the stethoscope* Q

***Causes of Physiological and Pathological Third Heart Sounds (S3)***

**Third Heart Sound ($S_3$): Ventricular Diastolic Gallop, Protodiastolic Gallop, and Pericardial Knock**

| Physiologic $S_3$ | Pathologic $S_3$ |
|---|---|
| • Children<br>• High cardiac output<br>- ***Atheletes*** Q<br>- *Fever* Q<br>- *Pregnancy* Q<br>- *Thyrotoxicosis* Q<br>- *AV fistulas* Q | • ***Ventricular dysfunction (LVF/RVF)*** – poor systolic function, increased end-diastolic and end-systolic volume, decreased ejection fraction, and high filling pressure.<br>- Idiopathic dilated cardiomyopathy<br>- *Ischemic heart disease*<br>- Valvular heart disease<br>- Congenital heart disease<br>- Systemic and pulmonary hypertension<br>• Excessively rapid early diastolic ventricular filling<br>- Hyperkinetic states<br>- Anemia<br>- Thyrotoxicosis<br>- Arteriovenous fistula<br>- Atrioventricular valve incompetence<br>- ***Left to right shunts (VSD, PDA and ASD)***<br>• Restrictive myocardial or pericardial disease<br>• ***Constrictive pericarditis (pericardial knock)***<br>• Restrictive cardiomyopathy<br>• Hypertrophic cardiomyopathy. |

**Pathological Third Heart Sound (S3) may be associated with Constrictive Pericarditis**

Constrictive pericarditis is characterixstically associated with pericardial knock which is a distinct form of third heart sound ($S_3$)

***'Pericardial knock is $S_3$ that occurs earlier*** *(0.1 to 0.12 after A2) and is higher pitched than normal. Its presence depends upon the restrictive effects of the adherent pericardium which halts diastolic filling abruptly' – Harrison*

### Congenital Heart Diseases associated with Loud S3

| Congenital Heart Diseases associated with Loud S3 |
|---|
| • *Ventricular septal Defect (VSD)* Q |
| • *Patent Ductus Arteriosus (PDA)* Q |
| • *Atrial Septal Defect (ASD)* Q |

## Fourth Heart Sound (S4)

- Fourth Heart sound occurs in association with an *effective atrial contraction*[Q]
  *(It is presumably caused by inrush of blood into the ventricles when the atria contracts and hence it is also called the 'Atrial Heart Sound')*
- ***It is heard during the ventricular filling phase of the cardiac cycle (Presystolic[Q] heart sound)***
- ***It is low pitched (frequency usually 20 cycle/sec or less-****(Guyton)*
- ***It is not audible to the unaided ear***
  Normally the fourth heart sound can almost never be heard even with a stethascope because of its weakness and low frequency *(Guyton)*
- S4 becomes audible when diminished ventricular compliance increases the resistance to normal filling
  When audible the S4 is *best heard with the bell of the stethescope*[Q]
- Loudest (Best heard) at the Left ventricular Apex when the patient is in left Lateral position
- It is accentuated by mild isotonic or isometric exercises in the supine position



**Causes of Pathological Fourth Heart sound**

**Fourth Hearth Sound (S4), Atrial Diastolic gallop, and Presystolic Gallop:**

**Decreased ventricular compliance**

- Ventricular hypertrophy
  - Left or right ventricular outflow obstruction
  - Systemic or pulmonary hypertension
  - Hypertrophic cardiomyopathy
- Ischemic heart disease
  - Angina pectoris
  - Acute myocardial infarction
  - Old myocardial infarction
  - Ventricular aneurysm
- Idiopathic dilated cardiomyopathy

**Excessively rapid late diastolic filling secondary to:**

- Vigorous atrial systole
- Hyperkinetic states
  - Anemia
  - Thyrotoxicosis
- Arteriovenous fistula
- Acute atrioventricular valve incompetence

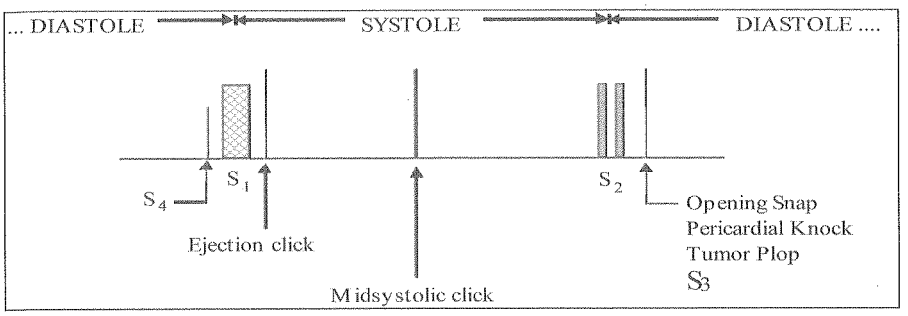
**Arrhythmias**

- Heart block

**Note:**

***Physiologic S4 may be recordable*** in patients with increasing age ***but is rarely audible***

## Added Heart Sounds




### Diastolic vs Systolic added Heart Sounds

**Added Heart Sounds**

| Diastolic sounds | Systolic sounds |
|---|---|
| • *Opening snap* [Q]<br>• *Third Heart sound (S3)* [Q]<br>• *Fourth Heart sound (S4)* [Q]<br>• *Pericardial knock* [Q]<br>• *Tumor plop (Atrial myxoma)* [Q] | • *Ejection sound/click* [Q]<br>• *Non ejection click/mid systolic click* [Q] |

### Location of Added Heart Sounds in systole/diastole

| Shortly after S1 [Q] | Shortly before S1 [Q] | Between S1 & S2 [Q] | Shortly after S2 [Q] |
|---|---|---|---|
| *Ejection click* | *Fourth heart sound* | *Midsystolic click* | *Opening snap*<br>*Pericardial knock*<br>*Tumor plop*<br>*S3* |

### Features of Added Sounds

| Ejection Click | Opening Snap | Pericardial knock | Tumor Plop |
|---|---|---|---|
| • *Sharp, High pitched sound* [Q] | • Brief, *High pitched sound* [Q] | • A third heart sound that is *higher pitched than normal* (S3 is low pitched). | • Tumor plop is a characteristic *low pitched sound* [Q] |
| • Audible during *early systole* [Q] *(Immediately after S1)* | • Audible during *early diastole* [Q] *(Between 0.04 to 0.12 sec after A2)* | • Audible during *early diastole* [Q] *(Within 0.01 to 0.12 sec after A2)* | • Audible during *early or mid diastole* [Q] |
| • *Seen in Aortic stenosis* [Q], *Pulmonary stenosis* [Q], *Hypertension* [Q] *and is produced due to sudden opening of semilunar valves in conditions where this opening is delayed.* | • *Seen in stenosis of AV valves (Mitral stenosis* [Q] > Tricuspid stenosis) | • Seen in *constrictive pericarditis* [Q] and produced due to sudden deceleration of venticular filling because of restrictive effect of adherent pericardium. | • Seen in conditions like *atrial myxoma* [Q] and produced due to the tumor abruptly stopping as it strikes the ventricular wall |

*Opening Snap*

***Opening snap***

- ***Brief high pitched sound***
- *Heard in early **diastole** (Ejection sound are heard in systole)*
- *It is usually due to **stenosis of an (A.V.)** most often mitral value.*
- *It **follows second heart sound,** $A_2$ by 0.05 to 0.12 sec.*
- *It is generally best heard at **lower left sternal border** and radiates well to the base of heart*
- *It is best heard during expiration*
- *The time interval between $A_2$ and $O_s$ varies inversely with the severity of M.S.*
- *It is followed by low pitched rumbling diastolic murmur*

***Opening snap indicates that :***

- *M.S. is organic (and significant)* Q
- *Valve cusps are pliable* Q
- *High atroventricular pressure gradient is present* Q
- *Severe, AR, MR, AF, SABE are absent.* Q

**Note:**

- *O.S. may also be audible in tricuspid stenosis*
- *O.S. of tricuspid stenosis occurs later in diastole than the mitral O.S*

## Cardiac Murmurs

### Classification and Types of Systolic murmurs

| Holosystolic /pan systolic murmurs | Midsystolic murmurs ejection systolic murmurs | Early systolic murmurs |
|---|---|---|
| ***Begin with $S_1$ and end after $S_2$***<br>• VSD<br>• Mitral Regurgitation<br>• Tricuspid Regurgitation<br>• Aortopulmonary shunts | ***Starts shortly after $S_1$ and ends before $S_2$***<br>**Aortic**: Aortic stenosis, Coarctation, Aneurysm, PDA, High output states<br>**Pulmonary**: P. stenosis, P. hypertension, P. artery dilatation, ASD, High output states | ***Begin with first heart sound and end in midsystole***<br>• VSD<br>- Large VSD with pulmonary hypertension<br>- *V. small muscular VSD*<br>• ***Tricuspid regurgitation*** in absence of Pul. Hypertension<br>• Mitral regurgitation in a non compliant left atrium as in ***papillary muscle dysfunction*** |

### Differentiation of systolic murmurs base don changes in their intensity from physiologic maneuvers

| Maneuver | HOCM | AS | MR/VSD | MVP | TR | Flow |
|---|---|---|---|---|---|---|
| Valsalva's maneuver | ↑ | ↓ | ↓ | ↑ | ↓ | ↓ |
| Stand | ↑ | - | - | ↑ | - | ↓ |
| Squat | ↓ | - | - | ↓ | - | ↑ |
| Handgrip/TAO | ↓ | - | ↑ | ↑ | - | ↓ |
| Inspiration | - | - | - | - | ↑ | - or ↑ |
| Post-PVC | ↑ | ↑ | - | - | - | ↑ |

AS= aortic stenosis; Flow = benign flow murmur; HOCM = hypertrophic obstructive cardiomyopathy; MR = mitral regurgitation; MVP = mitral valve prolapse; PVC = pressure ventricular contraction; TAO = transient arterial occlusion; TR = tricuspid regurgitation; VSD = ventriocular septal defect; ↑ = increased in murmur intensity; ↓ = decreased in murmur intensity; - = no predictable change

## Murmur in Aortic Regurgitation :

| Typical **diastolic murmur** of Chronic AR | **Midsystolic** ejection murmur | Austin flint murmur **(diastolic)** |
|---|---|---|
| • High pitched, blowing, decrescendo diastolic murmur<br>• Heard best in the third I.C.S. along the left sternal border<br>Note: With marked post stenotic dilatation of aorta the murmur may be loudest in the 2nd or 3rd right interspace – *API 7th / 420* | • Resembles murmur of AS but is higher pitched, shorter and less rasping<br>• Heard best at the base of heart and is transmitted along the carotids | • Soft, low pitched rumbling middiastolic<br>• Heard best at the apex<br>• Produced by diastolic displacement of anterior leaflet of mitral valve by AR stream |

***Murmur of Mitral Stenosis***

*Low pitched[Q], rumbling[Q] diastolic murmur[Q] with 'Pre-systolic accentuation' heard best at the apex in left lateral recumbent position[Q].*

## Carey Coomb's Murmur and Austin Flint Murmur

**Carey Coomb's Murmur**

- Low pitched (soft)
- Delayed diastolic (Middiastolis)
- Mitral
- Associated with Acute Rheumatic carditis

**Attributed to :**

- Inflammation of mitral valve cusps
- Excessive left atrial blood flow as consequence of mitral regurgitation

**Austin Flint Murmur**

- Low pitched (soft)
- Delayed diastolic (Middiastolic / Late diastolic)
- Mitral
- Associated with Aortic Regurgitation

**Attributed to :**

- Anterior mitral valve leaflet when blood enters the left ventricle simultaneously from both the aortic route and the left atrium

*"**Carey Coomb's murmur is a delayed diastolic mitral murmur.**" - Ghai 6th / 376*

**Remember:**

*Low pitched, delayed diastolic mitral murmur in association with Rheumatic fever: Carey Coomb's murmur.*
*Low pitched, delayed diastolic mitral murmur is association with severe chronic AR: Austin Flint murmur.*

**Common condition producing acute MR include**

- Rupture of chordae tendnae
- ***Papillary muscle dysfunction*** or rupture following MI
- Infective endocarditis

## Causes of Continuous Murmurs

Causes of Continuous Murmur (Hurst)

**Continuous Murmur caused by Blood flow**

- Venous hum
- Mammary soufflé
- Hemangioma
- Hyperthyroidism
- Acute alcoholic hepatitis
- Hyperemia of neoplasm
  - hepatoma
  - renal cell carcinoma
  - paget disease

**Continuous murmurs caused by high-to low-pressure shunts**

Systemic artery to pulmonary artery
- Patient ductus arteriosus
- Aortopulmonary window
- Truncus arteriosus
- Pulmonary atresia
- Anamolous left coronary
- Bronchiectasis
- Sequestration of the lung

Systemic artery to right heart
- Ruptured sinus of Valsalva
- Coronary artery fistula

Left-to-right atrial shunting
- Lutembacher syndrome
- Mitral atresia plus atrial septal defect

Venovenous shunts
- Anomalous pulmonary veins
- Portosystemic shunts

Arteriovenous fistula (systemic or pulmonic)

**Continuous murmurs secondary to localized arterial obstruction**

- Coarctation of the aorta
- Branch pulmonary stenosis
- Carotid occlusion
- Celiac mesenteric occlusion
- Renal occlusion
- Femoral occlusion
- Coronary occlusion

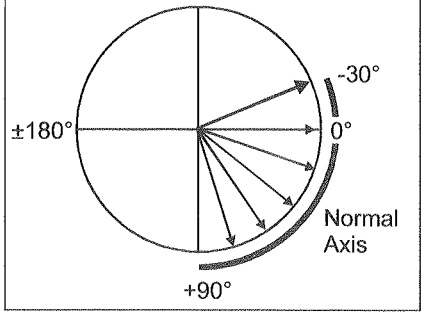
# ELECTROCARDIOGRAM (ECG)

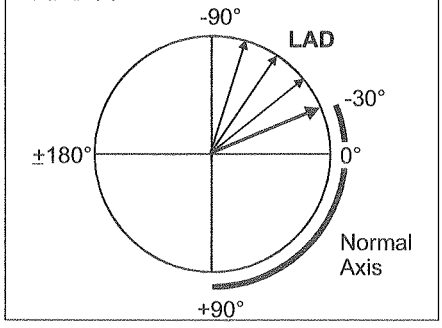
## The Cardiac Axis

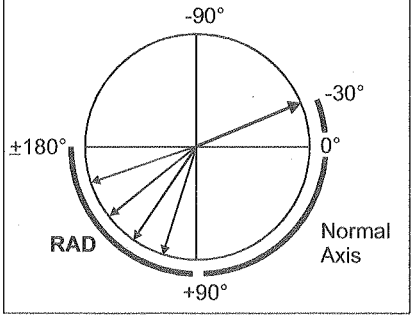
### The Cardiac Axis

- The cardiac axis refers to the mean direction of the wave of ventricular depolarization in the vertical plane measured from a zero reference point
- The zero refrence point looks at the heart from the same view point as lead I
- An axis lying above this line is given a negative number while an axis lying below this line is given a positive number
- *Theoretically the cardiac axis may lie anywhere between +180 to -180*

| Normal AXIS | Left Axis Deviation | Right Axis Deviation |
|---|---|---|
| Normal cardiac axis flows down and towards the left lower aspect of the heart between – 30 and +90 | Cardiac axis flow is upward and towards the left upper half of the heart between -30 and -90 | Cardiac axis flow is downwards and towards the right part of the heart between +90 and +/- 180 |




Extreme Right Axis Deviation
When flow of cardiac axis is upward and to the right between +/-180 and -90

- The standard cardiac axis is determined using Lead I and Lead II

| Normal Axis | Left Axis Deviation | Right Axis Deviation |
|---|---|---|
| -30 to +90<br>Positive in Lead I<br>Positive in Lead II | -30 to -90<br>Positive Lead I<br>Negative in Lead II | +90 to ±180<br>Negative in Lead I<br>Positive or Negative in Lead II |

- The Cardiac Axis in Different Leads

| | Normal Axis | Right axis deviation | Left axis deviation |
|---|---|---|---|
| Lead I | Positive | Negative | Positive |
| Lead II | Positive | Positive or negative | Negative |
| Lead III | Positive or negative | Positive | Negative |

| Note: |
|---|
| Lead I : POSITIVE BETWEEN -90 TO +90 (CLOCKWISE)<br>Lead II : POSITIVE BETWEEN -30 TO +150 (CLOCKWISE)<br>Lead III : POSITIVE BETWEEN +30 TO -150 (CLOCKWISE) |

## QRS Complex Voltage

### Low QRS voltage on ECG

- Diagnostic criteria for Low QRS voltage include QRS complex amplitude < 5mm in all limb leads (*when this is the case the amplitude in each of the precordial leads (V) is usually less than 10 mm, but this is not necessary for the diagnosis)*

| Low QRS voltage or ECG |
|---|
| *QRS amplitude <5 mm on all limb leads* |
| *QRS amplitude < 10 mm on all precordial leads* |

- Low QRS voltage should be considered a description and not a diagnosis (it may be a normal variant)

**Low Voltage on ECG**

| Stuff Between the surface and Heart | 'Less Heart' (↓Cardiac muscle) (Not true Hypertrophy) | Miscellaneous |
|---|---|---|
| • Obesity<br>• Chronic Obstructive Lung Disease (Emphysema)<br>• Pleural Effusion<br>• Pericardial effusion (Constrictive Pericarditis) | • Infiltrative Cardiomyopathy (Amyloidosis; Hemochromatosis)<br>• Dilated Cardiomyopathy<br>• Ischaemic Cardiomyopathy | • Hypothyroidism (myxoedema) |

*The combination of low QRS voltage plus a thick left ventricle on echocardiogram strongly suggests the diagnosis of infiltrative cardiomyopathy like cardiac amyloidosis. The increased thickness is the amyloid. It is not muscle (not true hypertrophy), does not depolarize and therefore adds nothing to QRS voltage.*

## QRS Complex Duration

**QRS Complex Duration**

| < 0.10 sec (< 100 m sec) | (Between 0.10 to 0.12 sec) Between 100 and 120 msec | > 0.12 sec (>120 m sec) |
|---|---|---|
| *Normal* | **Inpect for features of:**<br>1. *Incomplete RBBB*<br>2. *Left Anterior Fascicular Block*<br>3. *Left Posterior Fascicular Block*<br>*May be normal* | **Inspect for features of:**<br>1. *Right Bundle Branch block*<br>2. *Left Bundle Branch block*<br>3. *Intraventricular conduction delay (Hyperkalemia/Antiarrhythmics)* |

Any QRS complex Duration > 0.12 seconds is abnormal. There are no exceptions to this rule (A QRS complex Duration < 0.12 seconds may be normal)

## QRS complex: Wide or Narrow

- QRS complex represents ventricular depolarization and QRS interval represents the duration of ventricular depolarization.

  The normal QRS interval (QRS duration) is less than 0.10 to 0.11 seconds.

- If the QRS complex is less than 0.12 second, ventricular depolarization is more or less occurring normally over the His-Purkinje system.
- There are several causes for a wide QRS complex, which result from abnormal activation of the ventricles.
- ***Most commonly, a wide QRS complex is due to abnormal conduction over the right or left bundle due to block or delay of ventricular activation.***
- Rarely, a wide QRS complex is observed because the ventricles are being activated via both the His-Purkinje system and an accessory pathway.
- With greater use of cardiac devices, a wide QRS complex will be observed in patients with pacemakers where the ventricle is being activated artificially from an electrical impulse delivered via a ventricular pacing lead.

### Wide QRS complex with a normal rate: abnormal ventricular activation

| Condition | Pathophysiology | ECG findings |
|---|---|---|
| ***Bundle branch block*** | *Block in the right or left bundle leads to sequential activation of the right and left ventricles* | In right bundle branch block an rSR' will be seen in lead $V_1$ and in left bundle branch block a wide predominantly negative QRS complex will be seen |
| ***Accessory pathway*** | *The ventricles are activated by both the AV node and an accessory pathway* | The PR interval will be short due to early ventricular activation from the accessory pathway and the QRScomplex will be abnormal because of cell-to-cell activation of ventricular tissue |
| ***Hyperkalemia*** | *High levels of potassium lead to slow ventricular depolarization* | Prominent T waves will often be observed |
| ***Ventricular rhythm*** | *A site within the ventricles drives ventricular depolarization* | P waves will not precede the QRS complexes |
| ***Ventricular paced rhythm*** | *Similar to the ventricular rhythm* | A pacing artifact will be observed |

**Causes of QRS Widening ≥ 0.12 seconds (in decreasing order of mortality)**

- ***Hyperkalemia***
- ***Ventricular Tachycardia (Wide complex Tachycardia)***
- *Idioventricular Rhythm including heart blocks*

  *Wide QRS complex may be seen in Mobitz Type II second degree block and incomplete Third Degree Blocks but lacks certainity*

- *Drug effects and overdoses (especially Tricyclics)*
- ***Wolf Parkinson White syndrome***
- *LBBB; RBBB; Intraventricular conduction delay*
- *Ventricular premature contraction*
- *Aberrantly conducted complexes*

## QT Interval

**Abnormalities in QT interval**

***Prolonged***

*Conditions of the heart* ♀
1. Acute Rheumatic carditis
2. Myocarditis
3. Acute myocardial infarction
4. Mitral Valve Prolapse

*CNS insult*
Cerebrovascular accident

*Drugs*
- Antiarrythmics
  - Quinidine
  - Procainamide
  - Disopyramide
  - Sotalol
  - Amiadarone
- Phenothiazines
- Tricyclic Antidepressants
- Antibiotics
  - Erythromycin
  - Pentamidine
- Miscellaneous
  - Some antimalarials
  - Cispride
  - Probucol

*Hypothermia*

*Electrolyte*
- Hypocalcemia ♀
- Hypokalemic
- Hypomagnesemia

***Shortened***
- Hypercalcemia
- Digitalis therapy
- Vagal stimulation
- Hyperthermia

## ST Segment

**Abnormalities in ST segment are:**

*Elevated* ♀
- With convexity upwards → Acute MI ♀, LV aneurysm ♀, Prinzemetal angina ♀
- With concavity upwards → Acute pericarditis ♀

*Depressed* ♀
- Oblique Plane or Sagging → Coronary artery disease ♀ (Angina pectoris)
- With mirror image of a correction mark → Digitalis ♀
- With convexity upwards → In strain pattern of ventricular hypertrophy

## ECG Changes in Hypokalemia and Hyperkalemia

**ECG changes**

**Characteristic features of Hypokalemia**
- ***ST depression*** ♀
- ***Flattened or inverted T wave*** ♀
- ***Prominent U wave*** ♀
- Prolonged P-R interval ♀
- Prolonged QU interval (Real)
- Rarely S-A block

**Characteristic features of Hyperkalemia**

| | |
|---|---|
| Early | • Increased T wave amplitude ♀ Peaked T waves |
| Later (with severe degrees of hyperkalemia) | • Prolonged PR interval ♀<br>• Prolonged QRS duration ♀<br>• AV conduction delay<br>• Loss of P waves ♀<br>• Sine wave pattern ♀<br>• Ventricular fibrillation or asystole |

*Prominent U wave, ST segment sagging and T-wave flattening or inversion are characteristic features of Hypokalemia.*
*Hypokalemia may also present with a apparently prolonged QT interval on ECG. However this apparently prolonged QT interval is* in reality the QU interval that mimics a prolonged QT interval due to fusion of T-U waves.


Cardiovascular System

## ECG changes in Pneumothorax

### ECG Changes in left sided Pneumothorax

*ECG changed in pneumothorax, especially on the left, are important as there may mimic ECG, changes of acute MI*

**These include**

***Right ward deviation of QRS axis (Right axis deviation)***

*Decreased/absent R waves in the precordial leads*

*T wave inversion in precordial leads*

*Pathological Q waves*

*Decreased QRS voltage*

*Electrical alternans (alternating QRS amplitude with each heart beat)*

# Cardiac Arrhythmias

## Broad Complex Tachycardias vs Narrow complex Tachycardias

| **Ventricular tachycardia** (Broad complex tachycardia) | **Supraventricular tachycardia** *(Narrow complex tachycardia)* |
|---|---|
| • Ventricular rate > 100 bpm<br>• QRS duration > 0.12 sec. (>.14 sec.- Harrison)[Q]<br>• Cannot be relieved by carotid sinus massage. [Q] | • Ventricular rates > 100 bpm [Q]<br>• QRS duration < 0.12 sec.<br>• Can be relieved by carotid sinus message [Q] |

## Broad Complex Tachycardia

Broad Complex Tachycardia

**Ventricular Tachycardia**

VT is the most common cause of Broad complex tachycardia accounting for >80% of cases

**Supraventricular Tachycardia with abberancy**

SVT with abberancy accounts for 15-20% cases of broad complex tachycardia

Cause include

- SVT with a bundle branch block either LBBB or RBBB
- Atral flutter, Atrial fibrillation, AV reentrant tachycardia (AVRT) may also produce SVT with aberancy and result in wide complex tacycardia.

**Distinguishing Features between Broad complex tachycardia due to VT and SVT with aberrancy**

| **Differentiating features** | **Ventricular Tachycardia** | **Supraventricular Tachycardia with Abaerrancy** |
|---|---|---|
| • *QRS duration* | *Broad complex Tachycardia with QRS duration usually greater that 0.14 seconds*<br>*QRS ≥ 0.14 sec* | *Broad complex tachycardia with QRS duration usually between 0.12 sec to 0.14 seconds*<br>*QRS ≤ 0.14 sec.* |
| • *Fusion Beats* | *Characteristic of VT* | *Absent* |
| • *Capture Beats* | *Characteristic of VT* | *Unusual* |
| • *AV dissociation* | *Characteristic of VT* | *Absent* |
| • *Independent P waves* | *May be seen*<br>*Independent P waves when present are characteristic of VT and indicate AV dissociation* | *Independent P work's are not seen*<br>*P wave and QRS complex are linked to suggest that ventricular activation depends on atrial discharge* |
| • *QRS pattern* | *QRS pattern does not resemble /mimic typical LBBB or RBBB* | *QRS pattern often resembles /mimics typical LBBB or RBBB* |
| • *Axis (Frontal plane QRS)* | *Left axis deviation (< - 30°)* | *Normal or Right ward* |
| • *QRS morphology in V1* | *Monophasic or Biphasic* | *Triphasic* |
| • *R/S Ratio in V6* | *<1* | *>1* |
| • *Vagal manuvres* | *No effect* | *Slowing or termination of tachycardia by vagal manuvres* |

## ECG Features of Torsades de Pointes

**Characteristics of *Torsades de pointes***

- Polymorphic QRS complexes that change in amplitude
- Cycle length giving the appearance of oscillations around the baseline.
- Marked QT prolongation ℚ

## WPW Syndrome

### WPW syndrome : Accessory AV Pathways

- WPW syndrome or 'Prexcitation syndrome' is charachterized by the presence of *tachyarrythmias*ℚ due to an *accessory conducting pathway*ℚ between atrium and ventricle
- WPW abnormality occurs when an impulse reaches the atria or ventricles earlier than would be expected if the impulse traveled by way of normal specialized conducting tissue *(Pre excitation)* ℚ

| |
|---|
| - When atrial impulse activates the entire or some part of ventricle<br>- When ventricular impulse activates the entire or some part of the atrium |

### Epidemiology

- ***Incidence varies from 0.1 to 3.0/1000 in apparently healthy subjects (Average = 1.5/1000)***
- It may be found in all ages (Neonates to Elderly)
- Prevalence decreases with age apparently because of loss of preexcitation
- ***It is more common in Males***
- Most adults with WPW syndrome have normal heart
  (However various acquired and congenital defects may be associated specially Ebstein's anomaly, MVP and cardiomyopathics)

### Electrocardiographic features

Three basic features typify the ECG abnormalities with usual form of WPW syndrome

- Short PR interval (PR interval <120 ms during sinus rhythm)ℚ
- Wide QRS complex (>120 ms) with a slurred slowly rising upstroke (delta wave) ℚ
  *The terminal portion of QRS complex is usually normal as conduction through bundle of His usually catches up with preexcitation*
- Secondary ST-T changesℚ that are generally directed to an opposite direction to the major Delta/ QRS vectors

**Note**

- **Fusion beats**: ℚ If the accessory pathway is capable of anteprade conduction, the typical QRS complex represents a 'Fusion beat' as a result of depolarization of the ventricle in part by the wave travelling from the accessory pathway and in part by wave travelling from normal AV nodal pathway
- **Normal p wave**ℚ – Since the atrial activation is normal, the P wave is usually normal

## Cardiac Conduction Blocks

### First Degree AV Block

**First Degree AV Block**

First degree AV block is charachterized by a delay in conduction across the conducting tissue (prolonged PR interval)

**Features**

- *PR interval is prolonged (>0.20 seconds)*ℚ
- *PR interval is constant (at the prolonged duration)* ℚ
- *Rhythm is regular* ℚ
- *Each P wave is followed by a QRS complex* ℚ
- *QRS complex morphology / duration is usually normal* ℚ

## Second Degree AV block

### Second Degree AV Block

Second degree AV block is characterized by intermittent failure of conduction from atria to ventricles

#### Type I (Mobitz) / Wenchebeck Type

This is charachterized by progressive prolongation of PR interval prior to a non conducted P wave

**Features**

- *Atrial Rhythm regular* ♀
- *Ventricular Rhythm irregular* ♀
- *Atrial rate exceeds ventricular rate* ♀
- *PR internal varies* ♀
- *PR progressively gets longer until a QRS is dropped* ♀
- *QRS morphology is often normal* ♀

#### Type II (Mobitz)

This is charachterized by constant PR interval prior to a non conducted P wave

**Features**

- *Atrial Rhythm regular* ♀
- *Ventricular Rhythm Regular (unless conduction rations vary)* ♀
- *Atrial Rate exceeds ventricular rate* ♀
- *PR interval is constant* ♀
  *PR interval does not get progressively longer and a QRS is dropped suddenly*
- *QRS morphology is usually abnormal* ♀ *(rarely normal)*

## Third Degree AV Block

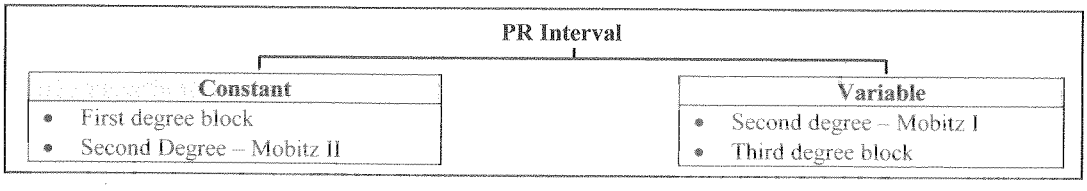
### Third Degree AV Block: Complete AV Block

Third degree AV block or complete AV block is charachterized by complete failure of conduction from atria to ventricles. (Atria and ventricles are under the control of separate pacemakers).

**Features**

- *Atrial Rhythm regular* ♀
- *Ventricular Rhythm regular* ♀
- *Atrial rate exceeds ventricular rate* ♀ *(The inherent rate of ventricular pacemaker is slower)*
- *PR interval varies* ♀ *(variable)*
- *P waves have no constant relationship to QRS complexes* ♀ *(AV dissocation)*
- *QRS complex morphology may be abnormal* ♀

### AV Blocks classified based on PR Interval




| **PR constant (First-degree)**<br>**(First-degree)** | **PR varies**<br>**(Second-degree, Mobitz 1)** |
|---|---|
| *PR constant* | *PR varies* |
| *PR prolonged* | *PR progressively gets longer until a QRS is dropped* |
| *Regular atrial rhythm;*<br>*Regular ventricular rhythm* | *Regular atrial rhythm;*<br>*Irregular ventricular rhythm* |
| **(Second –degree, Mobitz II)** | **(Third- degree)** |
| *PR constant* | *PR varies* |
| *PR normal or prolonged*<br>*Two or three P waves (possibly more) to each QRS* | *P waves have no constant relationship to QRS (found hidden in QRS complexes and T waves)* |
| Regular atrial rhythm;<br>Regular ventricular rhythm (unless conduction ratios vary) | *Regular atrial rhythm;*<br>*Rgular ventricular rhythm* |

## AV CONDUCTION BLOCKS: Review

| Name | Rhythm | Rate (beats/minute) | P waves (lead II) | PR Interval | QRS complex |
|---|---|---|---|---|---|
| First-degree atrio-ventricular (AV) block | Regular | That of underlying sinus rhythm; both atrial and ventricular rates will be the same | ***Sinus origin; one P wave to each QRS complex*** | Prolonged (more than 0.20 second); remains constant | Normal (0.10 second or less) |
| Second-degree AV block, Mobitz I | Atrial: regular<br>Ventricular: irregular | Atrial: that of underlying sinus rhythm<br>Ventricular: depends on number of impulses conducted through AV node: ***will be less than atrial rate*** | Sinus origin | Varies; progressively lengthens until a P wave isn't conducted (P wave occurs without the QRS cmplex); a pause follows the dropped QRS complex | Normal (0.10 second or less) |
| Second-degree AV block, Mobitz II | Atrial: regular<br>ventricular: usually regular, but may be irregular if conductions ratios vary | Atrial: that of underlying sinus rhythm<br>Ventricular: depends on number of Impulses conducted through AV node; will be ***less than atrial rate*** | Sinus origin: two or three P waves (sometimes more) before each QRS complex | Normal or prolonged; remains constant | Normal if block at level of bundle of His;<br>***Wide if block in bundle branches*** |
| Third-degree AV block | Atrial: regular<br>Ventricular: regular | Atrial: that of underlying sinus rhythm<br>Ventricular:40 to 60 if paced by AV junction; 30 to 40 (sometimes less) if paced by ventricles; will be less than atrial rate | Sinus P waves with ***no constant relationship to the QRS complex***; P waves found hidden in QRS complexes and T waves | Varies greatly | Normal if block at level of AV node or bundle of His; wide if block in bundle branches |

*No constant Relationship between P wave and QRS complex is a feature of Third degree or complete heart block.*
*One P wave to each QRS complex is a feature of First degree block*

# Heart Failure

## Features of Left Heart Failure and Right Heart Failure

### Left heart failure

- Left heart failure is defined as a clinical syndrome where the dominant feature is fluid congestion in the lungs (pulmonary) rather than in the systemic circulation
- The pulmonary capillary wedge pressure is typically elevated (↑PCWP)
- Predominant symptoms are related to passive congestion of lungs and pulmonary edema
- Dyspnea
- Orthopnea
- Paroxysmal Nocturnal Dyspnea (PND)
- Cough with Pink Frothy Sputum
- Rales / Crackles

### Right heart failure

- Right heart failure is defined as a clinical syndrome where the dominant feature is fluid congestion in the systemic circulation.
- The pulmonary capillary wedge pressure is normal (Normal PCWP) unless Right heart failure is caused secondary to left sided heart failure (↑ed PCWP)
  ***(PCWP is not elevated in isolated Right heart failure)***
- Predominant symptoms are related to passive systemic congestion
- Peripheral Edema
- Ascitis
- Congestive hepatomegaly (may be pulsatile)
- Congestive splenomegaly
- Weight gain
- Nocturia
- Raised JVP
- Positive Hepatojugular reflex

# Valvular Heart Diseases

## Mitral stenosis

### Auscultatory findings and Xray Features of Mitral Stenosis

**Mitral stenosis**

**Auscultatory findings**

- **$S_1$ :** *accentuated.*
- **$S_2$ :** *Normally split $S_2$ with accentuated $P_2$* [Q]
- **Murmur :** *Low pitched* [Q], *rumbling* [Q] *diastolic murmur* [Q] *with 'Pre-systolic accentuation' heard best at the apex in left lateral recumbent position* [Q].
- **Opening snap:** *brief, high pitched* [Q], *early diastolic* [Q] *sound, best heard at the lower left sternal border* [Q].

**X Ray findings**

- *Straightening of the left border of cardiac silhouette* [Q]
- *Prominence of main pulmonary artery* [Q]
- *Dilation of upper lobe pulmonary veins* [Q]
- *Kerley B lines* [Q] ✓
- *Backward displacement of the esophagus* [Q]

### Features Suggesting severity of Mitral Stenosis

**Features suggesting severe MS are :**

1. *Proximity of S2 - O.S. gap* [Q], *and*
2. *Longer duration of mid-diastolic murmur* [Q]

## Mitral Regurgitation

### Features Suggesting severity of Mitral Regurgitation

Severity of Mitral Regurgitation : Features indicating increased severity:

- ***Presence of Left ventricular $S_3$ or an inflow rumble at the apex***
- *Harsh Decrescendo murmur with lot of low and medium frequencies*
- *Wide split $S_2$ due to early $A_2$ (not caused by $P_2$ delay) in presence of MR*

## Mitral Valve Prolapse (MVP)

**Mitral Valve Prolapse Review**

- Also known as *'Barlow's syndrome'* [Q] *or 'Billowing mitral valve'* [Q] *or 'Floppy valve syndrome'* [Q].
- It is most common in *females* [Q]
  Most commonly seen in young adults (15 to 50 years)
  (MVP may be seen in older individuals > 50 yrs. When seen in older individuals most patients are males and MR is more common and severe and requires surgical treatment)
- Inheritance in familial cases is *autosomal dominant* [Q].
- Clinical course is usually benign
  - Patients are *usually asymptomatic* [Q]
  - Patients may present with *non specific chest pain, dyspnea, fatigue and palpitations.* [Q]
- Auscultatory findings are characteristic and most important :
  - Characteristic *mid systolic* [Q] or late systolic *non ejection* [Q] *clicks* [Q] which may be *multiple* [Q]
  - Late systolic ejection murmur (Often but not always)
  - Accentuation of findings by *Valsalva and standing.* [Q]
  - Diminished by *squatting and isometric exercises.* [Q]
- Diagnosis :
  - *Investigation of choice is echocardiography.* [Q]
  - *ECG in most cases is normal.* [Q]

- Pathological Findings:
  - ***Myxomatous degeneration of mitral valve (less commonly in tricuspid and aortic valves)***
  - Elongated, Redudant or Ruptured chordae tendinae
    (patients with ruptured chordae tendinae are usually symptomatic with significant regurgitation – MR)
  - Dysfunction and ischaemia of papillary muscles
  - Progressive dilatation and calcification of mitral valve annulus
- Complications :
  - *M.R* $^{Q}$.
  - *Arrythmias* $^{Q}$
  - *Sudden death* $^{Q}$
  - *Transient ischemic attack* $^{Q}$
  - *Infective endocarditis* $^{Q}$

## Atherosclerosis

### Major Risk Factors for Atherosclerosis

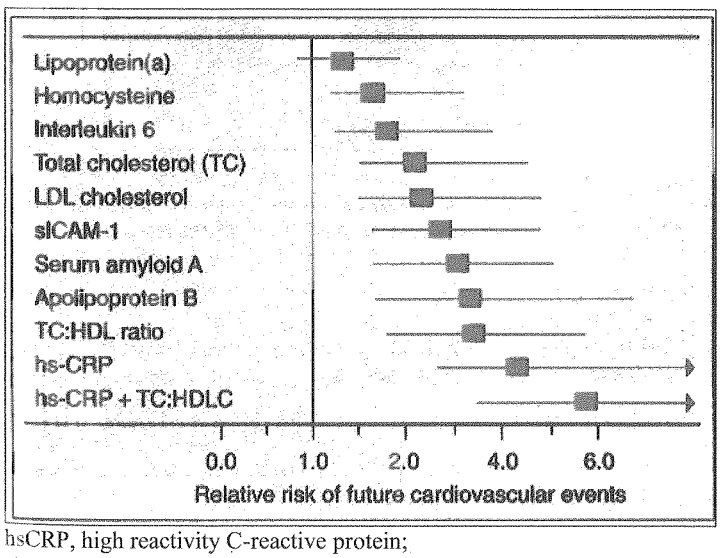
Major risk Factors for Atherosclerosis - *Harrisons*

- *Cigarette smoking*
- *Hypertension (BP > 140/90mm/hg) or (on Antihypertensive medication)*
- ***Low HDL cholesterol***
- Diabetes mellitus
- Family history of CHD
- Age (Men > 45 years; Women ≥ 55 years)
- Life style risk factors
  - Obeity (BMI > 30 kg/m$^2$)
  - Physical inactivity
  - Atherogenic diet

Emerging risk factors

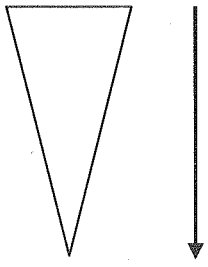
- Lipoprotein (a)
- ***Homocystine***
- Prothrombotic factors (Fibrinogen)
- Pro inflammatory factors
- Impaired fasting glucose
- Subclinical atherogenesis

### Risk Factor and Relative Risk of Future Cardiovascular adverse events




hsCRP, high reactivity C-reactive protein;
siCAM-1, soluble intercellular adhesion molecule-1;
HDLC, high density lipoprotein cholesterol

## Lipid Fractions and Relative Risk of Future Cardiovascular adverse events

| Relative risk for future cardio vascular events | Lipid Fractions and Lipid Ratios |
|---|---|
|  Decreasing Predictivity of Risk | • *Total chotesterol: HDL Cholestrol Ratio (TC: HDLC)*<br>• *Apopratein B100: HDL Cholesterol Ratio (APo B100: HDLC)*<br>• *LDL Cholesteral : HDL Cholesterol Ratio (LDLC: HDLC)*<br>• *Apoprotein B100: Apoprotein A-1 (APO B100: APO A1)*<br>• *Non HDL Cholesterol fraction*<br>• *Apolipoprotein B-1 Fraction*<br>• *HDL cholesterol Fraction*<br>• *Total cholesterol Fraction*<br>• *Apolipoprotein A1 Fraction*<br>• *LDL cholesterol Fraction* |

## Type of Hyperlipidemia and Risk of Coronary Artery Disease

| Condition | Risk Of Coronary Artery Disease |
|---|---|
| *Type I (Familial Hyper Chylomicronemia)* | *Not increased* |
| Type II A (Familial Hyper Cholesterolemia) | Accelerated |
| Type II B (Familial Combined Hyperlipidemia) | Accelerated |
| Type III (Familial Dysbetalipoprotenemia | Accelerated |
| Type IV (Familial Hyper Triglyceredemia) | Accelerated |
| ***Type V (Familial Mixed Hypertriglyceredemia)*** | ***Not increased*** |

## Metabolic Syndrome

**Metabolic Syndrome is identified by the presence of any 3 of the following risk factors:**

| **Risk Factor** | **Defining Level** |
|---|---|
| Abdominal obesity*<br>Men<br>Women | Waist circumference†<br>>102 cm (>40 in)<br>>88 cm (>35 in) |
| Triglycerides | >150 mg/dL |
| HDL cholesterol<br>Men<br>Women | <br><40 mg/dL<br><50 mg/dL |
| Blood pressure | >130/>85 mmHg |
| Fasting glucose | >110 mg/dL |

** Overweight and obesity are associated with insulin resistance and the metabolic syndrome. However, the presence of abdominal obesity is more highly correlated with the metabolic risk factors than is an elevated body mass index (BMI). Therefore, the simple measure of waist circumference is recommended to identify the body weight component of the metabolic syndrome.*

*† Some male patients can develop multiple metabolic risk factors when the waist circumference is only marginally increased, e.g., 94-102 cm (37-39 in). Such patients may have a strong genetic contribution to insulin resistance. They should benefit from changes in life habits, similarly to men with categorical increases in waist circumference.*

# Myocardial Infarction

## Universal Defination of Myocardial infarction

**Universal Defination of Myocardial infarction**

| ***Myocardial infarction related to ischemia due to primary coronary event*** (plaque rupture) ***or imbalace between oxygen demand and supply*** (coronary spasm, hypotension etc) | ***Myocardial Infarction related Sudden Cardiac Death*** (Death occuring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood.) | ***Myocardial Infarction associated with PCI*** (in patients with normal baseline troponin values) | ***Myocardial infarction associated with CABG*** (in patients with normal baseline troponin values,) |
|---|---|---|---|
| Detection of rise and/or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99$^{th}$ percentile of the upper reference limit (URL) together with evidence of myocardial ischaemia with at least one of the following:<br>• Symptoms of ischaemia<br>• ECG changes indicative of new ischaemia [new ST-T changes or new left bundle branch block (LBBB)]<br>• Development of pathological Q waves in the ECG<br>• Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality. | *Sudden, unexpected cardiac death, involving cardiac arrest, often with :*<br>• ***Symptoms suggestive of myocardial ischaemia***, and accompanied by<br>• New ST elevation, or new LBBB, and/or<br>• Evidence of fresh thrombus by coronary angiography and/or at autopsy, | • ***By convention, increases of biomarkers greater than 3 x 99$^{th}$ percentile*** *URL have been designated as defining PCI-related myocardial infarction.* | • ***By convention, increases of biomarkers greater than 5 x 99$^{th}$ percentile*** URL plus either new pathological Q waves or new LBBB, or angiographically documented new graft or native artery occlusion, or imaging evidence of new loss of viable myocardium have been designated as defining CABG-related myocardial infarction. |

## Criteria For Prior Myocardial Infarction

| **Criteria for prior myocardial infarction** |
|---|
| Any one of the following criteria meets the diagnosis for prior myocardial infarction<br>• Development of new pathological Q waves with or without symptoms<br>• Imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract, in the absence of a non-ischaemic cause.<br>• Pathological findings of a healed or healing myocardial infarction. |

*Taken from :Expert Consensus Document Circulation 2007 (American Heart Association Journals); 'ECS-ACCF-AHA-WHF Universal Definition of Myocardial Infarction'; http://circ.ahajournals.org/content/116/22/2634.full.pdf*

## The frequency of critical narrowing of arterial trunks and corresponding sites of myocardial lesions

**The frequency of critical narrowing of arterial trunks**

| Common | Uncommon | Rare (Never Encountered) |
|---|---|---|
| • Left anterior descending (LAD) artery (40-50%)<br>• Right coronary artery (30-40%)<br>• Left circumflex coronary artery (15-20%) | • Left main coronary artery<br>• Secondary branches e.g.<br>- Diagonal branches of LAD artery<br>- ***Marginal branches*** | • Penetrating intramyocardial branches of coronary arteries |

| Left anterior discending (LAD) (Br. of LCA) 40 to 50% (Most common) | Right coronary artery (RCA) 30-40 % | Left circumflex (br. of LCA) 15 to 20% |
|---|---|---|
| *Anterior wall of L.V. near apex*<br>*Anterior portion of ventricular septum* | *Inferior/Posterior wall of L.V*<br>*Post. portion of ventricular septum*<br>*Inferior/posterior right ventricular free wall in some cases* | *Lateral wall of left ventricle except the apex* |

## Cardiac Enzymes and Myocardial Infarction

**Preferred Markers for Detection of Acute Myocardial Infarction (Specific)**

| Enzyme | Seen at | Peaks at | Returns to normal after | Other features |
|---|---|---|---|---|
| Creatinine phosphokinase (MB Isoenzyme) | 4 to 8 hours | 24 hrs | 48-72 hrs | • Very sensitive test<br>• Less specific than troponins (also increase in skeletal muscle injury)<br>• ***Test of choice for detecting recurrent ischemic event in 4 to 10 day window*** |
| Troponin I | 4 to 8 hours | 48 hours | 7-10 days | • Very Sensitive test (Sensitivity similar CPK-MB)<br>• Very Specific test (More specific than CPK-MB).<br>• ***Test of choice for detecting Acute Myocardial Infarction (Early diagnosis and Late Diagnosis)***<br>• ***Less useful for detecting re-infarction since troponins may remain elevated for 10-14 days making it*** |
| **Troponin T** | **4 to 8 hours** | **48 hours** | **10-14 days** | |

**Non Specific Markers for Detection of Acute Myocardial Infarction ( Not Preferred)**

| Enzyme | Seen at | Peaks at | Returns to normal after | Other features |
|---|---|---|---|---|
| Myoglobin | 30 minutes to 2 hours | 4-6 hours | 10 to 12 hours | ***Earliest Marker to be raised***<br>Not specific for MI |
| Lactate dehydrogenase | 24 hrs | 4-5 days | 10 days | Not Specific |
| AST or SGOT | Within 12 hrs | 48 hrs | 4-5 days | Not specific |

## Management of Myocardial Infarction

Myocardial Infarction

**ST Elevation MI (STEMI)**

Immediate Management with MONA
- Morphine
- Oxygen
- Nitrates
- Aspirin

Start Adjunctive Treatment
- Beta Blockers (IV)
- Nitroglycerine (IV)
- Heparin (IV)

Reperfusion Therapy is the definitive treatment of choice if patient present <12 hours.
- Thrombolysis (Streptokinase)
- Early Primary PCI

Presentation > 12 hrs of chest pain:
**No thrombolysis** (Thrombolysis has no use)

**Non ST Elevation MI (NSTEMI)**

Immediate Management with MONA
- Morphine
- Oxygen
- Nitrates
- Aspirin

Start Adjunctive Treatment
- Heparin (UFH/LMNH)
- Aspirin, clopidogrel
- Nitroglycerine (IV)
- Beta blockers

Revascularisation Therapy is the definite treatment of choice in all 'High Risk Patients'
- Early Primary PCI

Thrombolysis is contraindicated

# Cardiomyopathy

**Symptomatic Cardiomyopathy**

| Dilated cardiomyopathy | Restrictive Cardiomyopathy | Hypertrophic cardiomyopathy |
|---|---|---|
| *Dominant Feature is systolic dysfunction* (contractile dysfunction) | *Dominant Feature is diastolic dysfunction* | *Dominant Feature is diastolic dysfunction* |
| ***Ejection Fraction <30%*** | **Ejection Fraction > 30-50%** | **Ejection Fraction >60%** |
| *'Decreased systolic function charachterizes dilated cardiomyopathy' - H18th* | *'Restrictive cardiomyopathy is dominated by abnormal diastolic function'- H18th* | *'Hypertrophic cardiomyopathy is characterized hemodynamically with diastolic dysfunction'- H18th* |

**Presentation with Symptomatic Cardiomyopathy:**

| Features | Dilated | Restrictive | Hypertrophic |
|---|---|---|---|
| **Ejection fraction (Normal 55%)** | Usually <30% | Usually >30 – 50% | Usually >60% |
| **Left ventricular diastolic dimension (Normal <55mm)** | >= 60 mm | <60 mm (May be decreased) | Often decreased |
| **Left ventricular wall thickness** | Decreased | Normal or increased | Markedly increased |
| **Atrial size** | Increased | Increased; may be massive | Increased |
| **Valvular regurgitation** | Related to annular dilation; Mitral appears earlier, during decompensation; Tricuspid regurgitation in late stages | Related to endocardial involvement; Frequent mitral and tricuspid regurgitation, rarely severe | Related to valve-septum interaction; Mitral regurgitation |
| **Common first symptoms** | Exertional intolerance | Exertional intolerance, Early fluid retention | Exertional intolerance; May have chest pain |
| **Congestive symptoms*** | Left before right, except right prominent in young adults | Right often dominates | Left-sided congestion may develop late |
| **Arrhythmia** | Ventricular tachyarrhythmia; Conduction block in Chagas' disease, and some families. Atrial fibrillation. | Ventricular uncommon except in sarcoidosis Conduction block in sarcoidosis and amyloidosis. Atrial fibrillation. | Ventricular tachyarrhythmias; Atrial fibrillation |

*Left-sided symptoms of pulmonary congestion: dyspnea on exertion, orthopnea, paroxysmal nocturnal dyspnea.
*Right-sided symptoms of systemic venous congestion: discomfort on bending, hepatic and abdominal distention, peripheral edema.

## Hypertrophic Obstructive Cardiomyopathy (HOCM)

**Distinctive Pathophysiological features include**

**Heterogeneous hypertrophy of LV**

**Septal Hypertrophy**

- Pattern of hypertrophy is distinctive
- ***Asymmetrical septal hypertrophy*** is characteristic
- Thickness of ventricular septum is disproportionately increased when compared with the free wall

**Dynamic LV outflow obstruction**

- Dynamic LV outflow obstruction: it is related to narrowing of the subaortic area as a consequence of opposition of anterior mitral valve leaflet against the hypertrophied septum in midsystole. The concept is termed ***systolic anterior motion (SAM)*** of mitral valve.
- Dystolic dysfunction: The ubiquitous pathophysiological abnormality is not systolic but rather ***diastolic dysfunction*** - *Harrison*

**Clinical spectrum of HOCM**

| Asymptomatic patient [Q] | Sudden death[Q] | Symptomatic patient |
|---|---|---|
| many patients are asymptomatic | Sudden death may be first clinical manifestation of disease (commonly seen in young adults after competitive sports) | |

| Symptoms | Signs | | |
|---|---|---|---|
| • Dyspnea[Q] is the commonest symptom<br>• Angina pectoris/chest pain[Q]<br>• Fatigue[Q]<br>• Syncope[Q] | • **Double or triple precardial impulse**[Q]<br>• **Brisk carotid upstroke** [Q]<br>(Rapidly rising carotid pulse) | • **Fourth heart sound**[Q] | **Systolic murmur**<br>(Hallmark of disease)<br>• Harsh[Q]<br>• Diamond shaped (crescendo decrescendo) [Q]<br>• Best heard at lower left sternal border as well as at apex[Q] |

| Condition which increase obstruction & intensity of murmur | Conditions which decrease obstruction & intensity of murmur |
|---|---|
| **Factors that increase myocardial contractility** | **Factors that decrease myocardial contractility** |
| • *Exercise*[Q] | • Beta blockers |
| • *Sympathomimetic Amines*[Q] | • Calcium channel blockers |
| • *Digitalis Glycosides*[Q] | **Factors which increase Ventricular volume** |
| **Factors which decrease Ventricular volume** | • *Augmentation of venous return by passive leg raising*[Q] |
| • *Valsalva maneuver*[Q] | • *Expansion of Blood Volume*[Q] |
| • *Sudden standing*[Q] | • *Supine **Position***[Q] |
| • *Nitroglycerine*[Q] | **Increased aortic impedance & afterload:** |
| • *Amyl nitrite*[Q] | • *Elevation of Arterial pressure by phenylephrine*[Q] |
| • *Tachycardia*[Q] | • *Sustained hand grip*[Q] |
| **Decreased aortic impedance & afterload** | • *Squatting* |

## Management of HOCM

- Avoidance of strenuous physical activity
- **Beta Blockers** should be the initial drug [Q] in symptomatic individuals. They reduce:
  - *Heart rate*
  - *Blood pressure*
  - *Stiffness of left ventricle*
  - *Fatal arrythmias*
- **Calcium channel Blockers**[Q] (verapamil and diltiazem) are alternative drugs.
  - They reduce-stiffness of ventricle
  - Elevated diastolic pressures
- **Amiadarone** may be used to reduce arrythmias.
- **Surgical myomectomy**

# Cardiac Tamponade, Constrictive Pericarditis, Restrictive Cardimyopathy and Right Ventricular MI

| Characteristic | Tamponade | Constrictive Pericarditis | Restrictive Cardiomyopathy | RVMI |
|---|---|---|---|---|
| ***Clinical*** | | | | |
| **Pulsus paradoxus** | **Common** | **Usually absent** | **Rare** | **Rare** |
| Jugular veins | | | | |
| Prominent y descent | Absent | Usually present | Rare | Rare |
| Prominent x descent | Present | Usually present | Present | Rare |
| **Kussmaul's sign** | **Absent** (Rare)[Q] | **Present** | **Present** | **Present** |
| Third heart sound | Absent | Absent | Rare | May be present |
| Pericardial knock | Absent | Often present | Absent | Absent |
| ***Electrocardiogram*** | | | | |
| Low ECG voltage | May be present | May be present | May be present | Absent |
| **Electrical alternans** | **May be present** | **Absent** | **Absent** | **Absent** |
| ***Echocardiography*** | | | | |
| Thickened pericardium | Absent | Present | Absent | Absent |
| Pericardial calcification | Absent | Often present | Absent | Absent |
| Pericardial effusion | Present | Absent | Absent | Absent |
| RV size | Usually small | Usually normal | Usually normal | Enlarged |
| Myocardial thickness | Normal | Normal | Usually increased | Normal |
| **Right atrial collapse and RVDC** | **Present** | **Absent** | **Absent** | **Absent** |
| Increased early filling, ↑ mitral flow velocity | Absent | Present | Present | May be present |
| Exaggerated respiratory variation in flow velocity | Present | Present | Absent | Absent |
| ***CT/MRI*** | | | | |
| Thickened/calcific pericardium | Absent | Present | Absent | Absent |
| ***Cardiac catheterization*** Equalization of diastolic procedures | Usually present | Usually present | Usually absent | Absent or present |
| Cardiac biopsy helpful? | No | No | Sometimes | No |

*RV, right ventricle; RVMI, right ventricular myocardial infarction; RVDC, right ventricular diastolic collapse; ECG, electrocardiograph.

**Note:**

*'A positive Kussmaul's sign is rare in cardiac tamponade. Its presence suggests that an organizing process and epicardial constriction are present in addition to effusion' – Harrisons

## Hypertensive Emergencies and Urgencies

Hypertensive Crisis

### Hypertensive Emergencies

- Marked elevation of Blood pressure with rapidly evolving end organ damage.
- No fixed Blood pressure cut off values are defined but, in general the blood pressure values are as follows.
  Diastolic BP> 120; Systolic BP>220
- Rapid /Immediate reduction of blood pressure is indicated in these patients
- Blood pressure should be controlled within hours (Preferably within 1 hours)
- Intensive monitoring in a critical care setting is mandatory

### Hypertensive urgencies

- Marked elevation of blood pressure without rapidly evolving end organ damage
- No fixed blood pressure cut off values are defined but in general the blood pressure values may approach the same range as seen in hypertensive emergencies
- Lowering of blood pressure is essential but immediate very rapid reduction is often not required
- Blood pressure should be controlled over a period of hours or days (Preferably within 24 hours)
- Intensive monitoring in a critical care setting is not always required

  *If the patient is asymptomatic or clinically stable the patient can be managed as an outpatient with dose follow up within days without an intensive monitoring setting usually with oval medications – Hurst 12th/1625*

Commonly used Drugs in the Management of Hypertensive Crisis

### Common Intravenous Agents (Used for Hypertensive Emergencies)

**Diuretics**

*Furosemide*

**Vosodilators**

*Sodium Nitroprusside*
*Nitroglycerine*
*Fenoldapam*
*Nicardipine*
*Hydralazine*
*Enolaprilant*

**Adrenergic Inhibitors**

*Phentolamine*
*Esmolol*
*Metaprolol*
*Labetolol*
*Urapidil*

### Common Oral Agents (Used for Hypertensive Urgencies)

*Nifedipine (Not Recommended now)*
*Nicardipine*
*Israpidine*
*Clonidine*
*Coptopril*
*Labetolol*
*Hydralazine*
*Nitroglycerine*

**** Nifedipine should be used with great caution 'if at all' according to the US F.D.A.'***

# Renovascular Hypertension/ Renal Artery Stenosis

Most common cause of Renovascular Hypertension

- **Elderly patients**
  - Atherosclerosis
- **Young patients**
  - **India**
    - Non specific Aorto-Arteritis (According to older editions)
    - Takayasu arteritis (According to latest editions)
  - **Western World**
    - Fibromuscular dysplasia

*The non specific aorto-arteritis causing renal artery stenosis is now believed to be Aorto-arteritis secondary to Takayasu arteritis*

## Renal Artery Stenosis: Review

- Renal Artery stenosis is an important cause of Renovascular Hypertension
- ***Bilateral involvement is seen in half of the affected cases (50%)***

## Etiology

- Atherosclerotic disease : This is the most common cause in middle aged /elderly patients
- Fibromuscular Dysplasia : ***This is the most important cause in young females***

## Presentation

- Hypertension
  - Abrupt onset of hypertension
  - Acceleration of previously well controlled hypertension
  - Refractory Hypertension
- Features of increased sympathetic neural activity (which is associated with Renovascular disease)
  - Flushing
  - Loss of nocturnal BP decrease
  - Putonomic instability
  - Rapid BP swings
- Progressive Renal failure / Azotemia

## Diagnosis

| Magnetic Resonance Angiography (MRA) | Contrast Enhanced Arteriography |
|---|---|
| MRA is the most sensitive (>90%) and specific (95%) non invasive test for the diagnosis of RAS | Contrast enhanced angiography is the most definitive (but invasive) diagnostic procedure for diagnosis of RAS |

## Management

**Medical Therapy with ACE Inhibitors or Angiotensin Receptor Blockers**

| Indications | Contra indications |
|---|---|
| **Unilateral Renal artery Stenosis**<br>- With hypertension & normal renal function (more effective than other antihypertensives)<br>- With hypertension & abnormal renal function (beneficial effect on survival without affecting renal function)<br>- With hypertension, diabetes, proteinuria and normal or abnormal renal function (effective antihypertensives) | **Bilateral Renal Artery stenosis**<br>ACE inhibitors or Angiotensin receptor blockers are contraindicated in patients with Bilateral renal artery stenosis or stenosis in a solitary kidney as their use in such patients leads to worsening of renal failure<br>(These patients are especially sensitive to decline in intraglomerular pressure) |

**Note**

***Acute Renal Failure / Worsening of Renal Failure with Angiotension Receptor Inhibitors is a diagnostic clue to the diagnosis of renal artery stenosis (indicates bilateral disease)***

**Surgical Therapy with Angioplasty + Stent placement**

*Should be considered only after optimal medical therapy has failed to achieve goal BP or resulted in a > 30% increase in serum creatinine*

## Basic Life Support

### Management of Cardiac Arrest

### Summary of Key BLS Components for Adults, Children, and Infants

(Excluding the new-born, in whom the etiology of an arrest is nearly always asphyxia)

| Component | Recommendations | | |
|---|---|---|---|
| | Adults | Children | Infants |
| | Unresponsive (for all ages) | | |
| Recognition | No breathing or no normal breathing (i.e. Only gasping ) | No breathing or only gasping | |
| | No pulse palpated within 10 seconds for all ages (HCP only) | | |
| **CPR sequence** | **C-A-B** | | |
| **Compression rate** | **At least 100/min** | | |
| Compression depth | At least 2 inches (5cm) | At least 1/3 AP diameter<br>About 2 inches (5cm) | At least 1/3 AP diameter<br>About $1^{1}/_{2}$ inches (4cm ) |
| Chest wall recoil | Allow complete recoil between compressions<br>HCP s rotate compressors every 2minutes | | |
| Compression interruptions | Minimize interruptions in chest compressions<br>Attempt to limit interruptions to < 10 seconds | | |
| Airway | Head tilt- chin lift<br>(If HCP suspects trauma use Jaw Thrust) | | |
| Compression-to –ventilation ratio (until advanced airway placed) | 3:2<br>1 or 2 rescuers | 30;2 Single rescuer<br>15:2 2HCP rescuers | |
| Ventilations; when rescuer untrained or trained and not proficient | Compressions only | | |
| Ventilations with advanced airway (HCP) | 1 breath every 6-8 seconds (8-10 breaths/min)<br>Asynchronous with chest compressions<br>about 1 second per breath<br>visible chest rise | | |
| Defibrillation | Attach and use AED as soon as available.<br>Minimize interruptions in chest compressions before and after shock;<br>Resume CPR beginning with compressions immediately after each shock. | | |

AED, automated external defibrillator; AP. Anterior-posterior; CPR, cardiopulmonary resuscitation; HCP, healthcare provider. .

## Cardiac Arrest

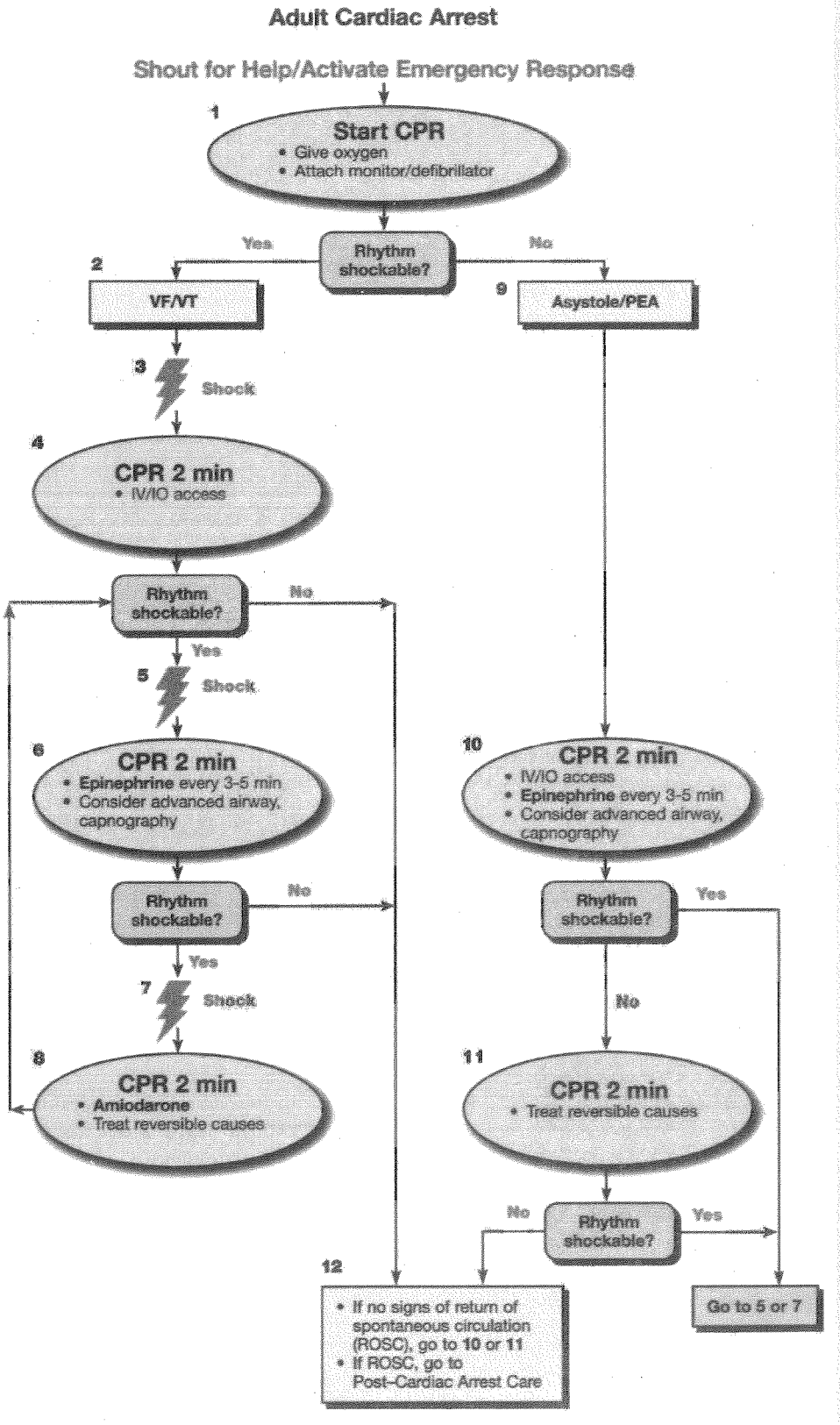
### ECG Rhythms in Cardiac Arrest

**ECG Rhythms in Cardiac Arrest**

| Shockable Rhythms<br>**(Urgent Drefibrillation is required)** | Non shockable Rhythms<br>**(Defibrillation is not indicated)** |
|---|---|
| • Ventricular Fibrillation<br>• Ventricular Tachycardia (Pulseless) | • Persistant/ Sustained Bradyarrhythmia<br>• Asystole<br>• Pulseless Electrical Activity (PEA)<br>(Electromechanical dissociation) |

*Electromechanical dissociation is the former terminology for PEA*

# ACLS Cardiac Arrest Algorithm (American Heart Association) 2010




**CPR Quality**
- Push hard (≥2 inches [5 cm]) and fast (≥100/min) and allow complete chest recoil
- Minimize interruptions in compressions
- Avoid excessive ventilation
- Rotate compressor every 2 minutes
- If no advanced airway, 30:2 compression-ventilation ratio
- Quantitative waveform capnography
  - If $P_{ETCO_2}$ <10 mm Hg, attempt to improve CPR quality
- Intra-arterial pressure
  - If relaxation phase (diastolic) pressure <20 mm Hg, attempt to improve CPR quality

**Return of Spontaneous Circulation (ROSC)**
- Pulse and blood pressure
- Abrupt sustained increase in $P_{ETCO_2}$ (typically ≥40 mm Hg)
- Spontaneous arterial pressure waves with intra-arterial monitoring

**Shock Energy**
- **Biphasic:** Manufacturer recommendation (eg, initial dose of 120-200 J); if unknown, use maximum available. Second and subsequent doses should be equivalent, and higher doses may be considered.
- **Monophasic:** 360 J

**Drug Therapy**
- **Epinephrine IV/IO Dose:** 1 mg every 3-5 minutes
- **Vasopressin IV/IO Dose:** 40 units can replace first or second dose of epinephrine
- **Amiodarone IV/IO Dose:** First dose: 300 mg bolus. Second dose: 150 mg.

**Advanced Airway**
- Supraglottic advanced airway or endotracheal intubation
- Waveform capnography to confirm and monitor ET tube placement
- 8-10 breaths per minute with continuous chest compressions

**Reversible Causes**
- Hypovolemia
- Hypoxia
- Hydrogen ion (acidosis)
- Hypo-/hyperkalemia
- Hypothermia
- Tension pneumothorax
- Tamponade, cardiac
- Toxins
- Thrombosis, pulmonary
- Thrombosis, coronary

# Coarctation of Aorta

**Clinical presentation :**

- Most patients are asymptomatic [Q]
- Symptomatic patients usually present with :
  - *Headache, dizziness,* [Q]
  - Epistaxis
  - *Cold extremities, and weakness in the legs* [Q]
  - ***Claudication with exercise*** [Q]
- Hypertension in upper extremities with marked diminution of pulsation in lower extremities. [Q]
- Mid systolic or continuous murmur over anterior part of chest and back [Q]
- Enlarged and pulsatile collateral vessels in intercostal spaces anteriorly in axilla or posteriorly in interscapular area[Q]
- Upper extremity and thorax may be more developed than lower extremities. [Q]

**Investigations :**

- ECG: shows L.V. Hypertrophy [Q]
- Radiography :
  - *Indentation of aorta at site of coarctation and '3 sign' on paramediastinal shaddon are almost pathogenic.* [Q]
  - *Notching* (erosion) of inferior surfaces of ribs. [Q]

**Complications :**

- Cerebral aneurysms and haemorrhage [Q]
- Rupture of aorta
- Left ventricular failure [Q]
- Infective endocarditis [Q]

**Treatment :**

- Is surgical *resection* [Q] of 'coarctation' and end to end anastomosis
  *Remember that HT may not be corrected even after surgical correction of the 'coarctation'.* [Q]

Few other questions :

| | | |
|---|---|---|
| *Most common site* [Q] of coarctation of aorta | : | *distal to origin of left subclavian artery.* [Q] |
| *Most common associated cardiac anomaly* [Q] | : | *bicuspid aortic valve.* [Q] |
| *May be associated with* [Q] | : | *Turner's syndrome.* [Q] |

***Associated anomalies with coarctation of Aorta*** [Q]

- **Bicuspid Aortic valve**[Q] **(commonest)**
- PDA[Q]
- VSD[Q]
- Tubular hypoplasia of aortic arch[Q]
- Aortic stenosis[Q] (valvular / subvalvular)

*Other Associated lesions that have been asked previously*

- Mitral valve abnormalities

(Subvalvular mitral ring /parachute mitral valve)

- Turner's syndrome[Q]

**Shone complex**[Q]

Coarctation of Aorta
+
Left sided obstructive lesions
*(Mitral valve abnormalities and subaortic stenosis)*

## Marfan Syndrome and associated Cardiac Lesions

Marfan's syndrome is a genetic disorder of the connective tissue of the body manifested principally by changes in the skeleton, eye and cardiovascular system

Mutation in the fibrillary gene [Q] (15 q 21.1) [Q]

↓

Loss of fibrillary fibre base for deposition of elastin

↓

Alteration in connective tissue in various parts of the body particularly in

**Skeletal changes of marfans syndrome:**

- *Patients are usually tall* [Q]
- *Have long limbs* [Q]
- *The ratio of upper segment to lower segment is usually* ***2 SDs below*** *the mean for age, race &sex*
- *Arachnodactyly (fingers are long and slender, spider like in appearance)* [Q]
- *Pectus Excavation, Pectum Carinatum.* [Q]
- *Scoliosis, Kyphosis* [Q]

**Cardiovascular changes** [Q]

- *Dmitral valve prolapse &* [Q]
- *Mitral valve progresses to* ***Mitral valve Regurgitation***
- *Aortic aneurysm occurs it can leads to* ***Aortic Regurgitation.***

- **Associated changes**
- *Spontaneous pneumothorax* [Q]
- *Inguinal & incisional hernias*
- *Striae may occur over the shoulders & buttocks.*

**Ocular changes** [Q]

- *Dislocation of the lens* [Q]
- *Elongation of globe (Myopia)* [Q]
- *Retinal detachment.* [Q]

## Atrial Myxoma

| **Sporadic myxomas:** | **Familial myxomas:** |
|---|---|
| • Are solitary [Q] | • Are multiple [Q] |
| • Located in Atria, most commonly in the left [Q] | • More likely to have post op recurrence [Q] |
| • Unlikely to have post-op recurrence [Q] | |
| • Occur in younger individuals [Q] | |

Presentation is highly dependent on position of tumour and hence it is intermittent and sudden in onset.
*(As a result of changes in tumor position with gravity).*

| **Cardiac signs and symptoms** | **Non cardiac signs and symptoms** |
|---|---|
| - Picture of Mitral valve disease | - **Peripheral or pulmonary emboli** [Q] |
| - Characterised by low pitched sound– 'tumor plop' [Q] (audible during early or mid diastole). | - **Fever** : Prolonged pyrexia of unknown origin [Q] |
| | - **Clubbing** [Q] |
| | - Raynaud's Phenomenon [Q] |
| | - Anemia/polycythemia or thrombocytopenia / thrombocytosis Leucocytosis |
| | - Elevated ESR [Q] |
| | - Rash [Q] |
| | - Weight loss, cachexia, malaise, arthralgia |

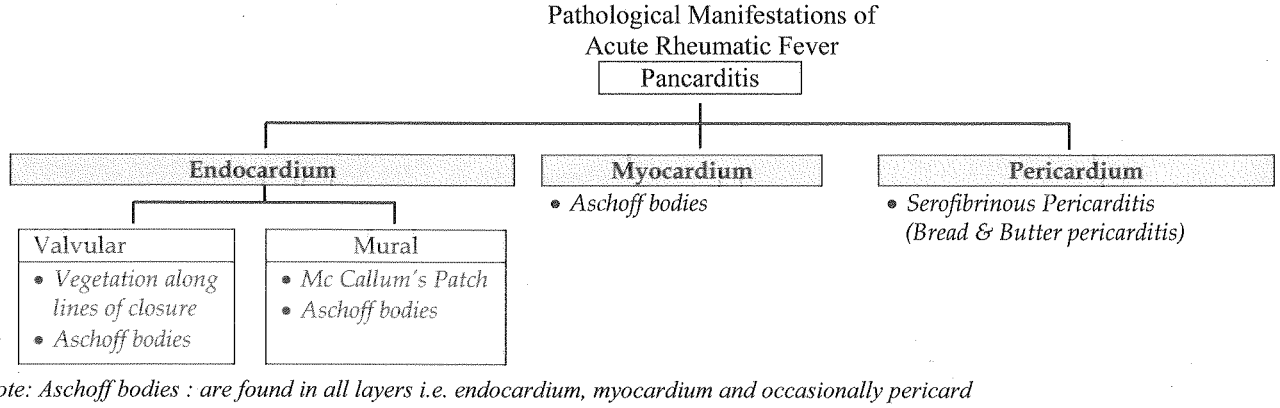
# Rheumatic Fever

## World Health Criteria for the diagnosis of Rheumatic fever

| World Health Criteria for the diagnosis of Rheumatic fever and rheumatic heart disease | |
|---|---|
| **Major manifestations** | • *Carditis*<br>• *Polyarthritis*<br>• *Chorea*<br>• *Erythema marginatum*<br>• *Subcutaneous nodules* |
| **Minor manifestations** | • Clinical: fever, polyarthralgia<br>• Laboratory: elevated erythrocyte sedimentation rate or leukocyte count<br>• Electrocardiogram: prolonged P-R interval<br>*@1992 Revised Jones criteria do not include elevated leucocyte count as a laboratory minor manifestation (but do include elevated C-reactive protein)* |
| ***Supporting evidence of a preceding streptococcal infection within the last 45 days*** | • Elevated or rising anti-streptolysin O or other streptococcal antibody, or<br>• A positive throat culture, or<br>• Rapid antigen test for group A streptococcus, or<br>• Recent scarlet fever<br>*@1992 Revised Jones criteria do not include recent scarlet fever as supporting evidence of a recent streptococcal infection* |

| Diagnostic Categories | Criteria |
|---|---|
| ***Primary episode of rheumatic fever*** | *Two major or one major two minor manifestations plus evidence of preceding group A streptococcal infection* |
| ***Recurrent attack of rheumatic fever in a patient without established rheumatic heart disease*** | *Two major or one minor manifestations plus evidence of preceding group A streptococcal infection* |
| ***Recurrent attack of rheumatic fever in a patient with established rheumatic heart disease*** | *Two minor manifestations plus evidence of preceding group A streptococcal infection* |

## Pathological Manifestations of Acute Rheumatic Fever




*Note: Aschoff bodies : are found in all layers i.e. endocardium, myocardium and occasionally pericard*

# Infective Endocarditis

**The Duke Criteria for the Clinical Diagnosis of Infective Endocarditis:**

| Major Criteria |
|---|
| *1. Positive blood culture* |
| • Typical microorganism for infective endocarditis from two separate blood cultures<br>• Viridans streptococci, *Streptococcus gallolyticus*, HACEK group, *Staphylococcus aureus*, *or*<br>• Community-acquired enterococci in the absence of a primary focus, *or*<br>• Persistently positive blood culture, defined as recovery of a microorganism consistent with infective endocarditis from:<br>• Blood cultures drawn >12 h apart; *or*<br>• All of 3 or a majority of 4 separate blood cultures, with first and last drawn at least 1 h apart<br>• Single positive blood culture for *Coxiella burnetii* or phase I IgG antibody titer of >1:800 |
| *2. Evidence of endocardial involvement* |
| • ***Positive echocardiogram***[b]<br>• Oscillating intracardiac mass on valve or supporting structures or in the path of regurgitant jets or in implanted material, in the absence of an alternative anatomic explanation, *or*<br>• Abscess, *or*<br>• New partial dehiscence of prosthetic valve, *or*<br>• New valvular regurgitation (increase or change in preexisting murmur not sufficient) |
| **Minor Criteria** |
| 1. Predisposition: predisposing heart condition or injection drug use<br>2. Fever 38.0°C (100.4°F)<br>3. Vascular phenomena: major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, Janeway lesions<br>4. Immunologic phenomena: glomerulonephritis, Osler's nodes, Roth's spots, ***rheumatoid factor***<br>5. Microbiologic evidence: positive blood culture but not meeting major criterion as noted previously[c] or serologic evidence of active infection with organism consistent with infective endocarditis |

[a]Definite endocarditis is defined by documentation of two major criteria, of one major criterion and three minor criteria, or of five minor criteria.

[b] Transesophageal echocardiography is recommended for assessing possible prosthetic valve endocarditis or complicated endocarditis.

[c]Excluding single positive cultures for coagulase-negative staphylococci and diphtheroids, which are common culture contaminants, and organisms that do not cause endocarditis frequently, such as gram-negative bacilli.

***Note:*** HACEK, *Haemophilus* spp., *Aggregatibacter actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, *Kingella* spp.

**Risk of infective endocarditis in various lesions:**

| High Risk | Moderate Risk | Low Risk |
|---|---|---|
| • *Prosthetic heart value*<br>• *Tetralogy of fallot*<br>• *PDA*<br>• *A regurgitation*<br>• *A stenosis*<br>• *Coarctation of Aorta*<br>• *VSD*<br>• *Mitral regurgitation* | • *MVP + M.R.*<br>• *T. stenosis*<br>• *T. Regurgitation*<br>• *P. Stenosis*<br>• *M. Stenosis* | • *ASD*<br>• *MVP without MR* |

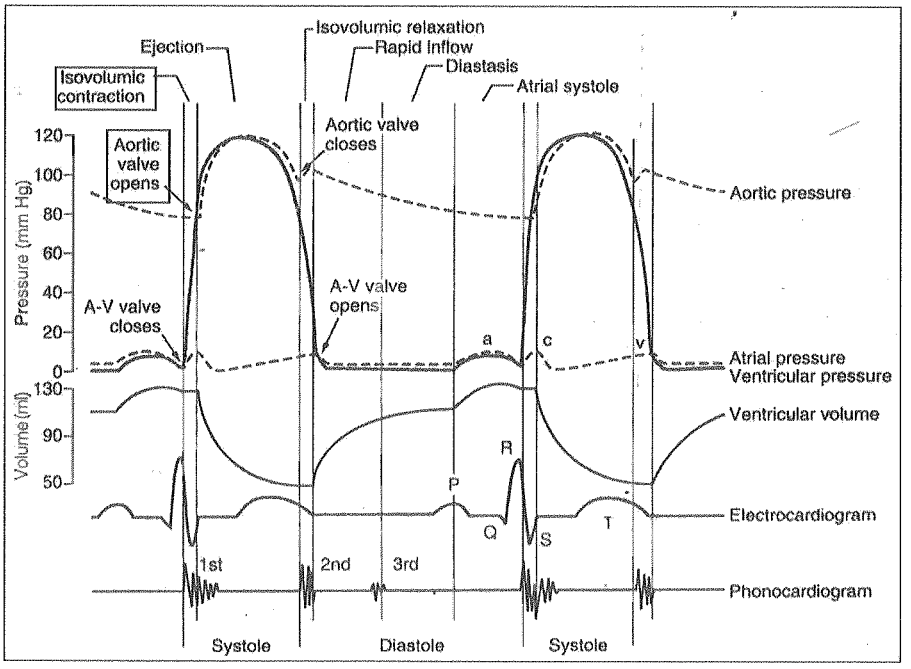
## Differetial Diagnosis of Vegetations in various Cardiac Lesions

| Rheumatic Fever | Non bacterial Thrombotic (Marantic Endocarditis) | Libman Sack's Endocarditis (SLE) | Infective Endocarditis |
|---|---|---|---|
| • Small<br>• Warty, verrucous<br>• Usually Firm<br>May be friable (but less than those of NBTE)<br>(embolization rare) | • Small (but larger than those of rheumatic)<br>• Friable<br>(embolization common) | • Medium sized(small)<br>• Flat, Verrucous,Irregular<br>• Usually Firm; occasionally friable<br>(embolization rare) | • Large, Bulky<br>• Irregular<br>• Friable *(most friable)*[Q]<br>(embolization common) |
| • Along lines of closure | • Along lines of closure | • On surface of cusps<br>Both surfaces may be involved most common being the undersurface, less often on mural endocardium<br>• In pockets of valves | • Irregular vegetations on valve cusps that can extend onto the chordae.<br>• Less often on mural endocardium |
| • Sterile (no organisms) | • Sterile | • Sterile | • Non-sterile (bacteria) |
| • Non destructive<br>Valve perforation : no<br>Mural involvement: rare | • Non destructive<br>Valve perforation : no<br>Mural involvement: rare | • Destructive<br>Valve perforation : no<br>Mural involvement: common | • Destructive<br>Ulcerates or perforates underlying valve (or myocardium) |
| • Seen in Rheumatic fever | • Seen in hyper coagulable states e.g. cancer, promyelocytic leukemia increased estrogenic state | • Seen in SLE | • Seen in Infective endocarditis |

***Most common site:***

- ***Most common site*** *for vegetations in Libman Sack's endocarditis are the A-V values, mitral and tricuspid.*
- ***Most common site*** *for vegetations in NBTE is mitral and less often aortic and Tricuspid.*
- ***Most common site*** *for vegetations of RF is mitral followed by combined mitral and aortic.*

# Cardiac Cycle




| Valvular event (valves) | Cardiac events | ECG | JVP (Jugular venous Pressure curve) |
|---|---|---|---|
| ***Opening of AV valve*** $^{Q}$ | ***End of isovolumic relaxation phase*** $^{Q}$ | ***End of T wave*** $^{Q}$ ***(phase b/w T wave and new p wave)*** | ***V-Y descent*** $^{Q}$ |
| Closure of AV valve | - End of diastole<br>- Beginning of isovolumic contraction | Later half of R wave | End of 'x' descent |
| Opening of semilunar valve | *End of isovolumic contraction* $^{Q}$ | ST segment | Peak of 'C' wave |
| Closure of semilunar valve | - Beginning of isovolumic relaxation phase<br>- Beginning of diastole | Later half of T wave | |

# QUESTIONS

## Arterial Pulses

### Pulsus Bisferiens

1. Pulsus bisiferiens is seen in all, EXCEPT:
   A. Aortic regurgitation + Aortic stenosis
   B. Aortic regurgitation *(AIIMS May 93)*
   C. Hypertrophic cardiomyopathy
   D. Tetralogy of Fallot
2. Bisfiriens pulse is seen in all Except: *(PGI Dec 05)*
   A. AS + AR
   B. AR
   C. Hypertrophic cardiomyopathy
   D. TOF
3. Pulsus bisferiens is best felt in :
   A. Carotid artery *(AIIMS Nov 98/ June 98)*
   B. Brachial artery
   C. Radial artery
   D. Femoral artery

### Pulsus paradoxus

4. Pulsus paradoxus is seen in all *except* :
   A. IPPV *(AIIMS June 98)*
   B. COPD
   C. Cardiac Temponade
   D. Constrictive pericarditis
5. Pulsus paradoxus is present in all Except:
   A. Emphysema *(PGI Dec 05)*
   B. Pulmonary embolism
   C. Hypovolemic shock
   D. Hypertrophic cardiomyopathy
6. True about pulsus paradoxus is – *(PGI June 98)*
   A. Arm-tongue circulation time is increased
   B. ↑ Stroke volume
   C. Seen in constrictive pericarditis
   D. ↑ HR
7. Pulsus paradoxus is seen in (select three correct options)– *(PGI June 06)*
   A. Cardiac tamponade
   B. Constrictive pericarditis
   C. HOCM
   D. AR
   E. Severe asthma

### Pulsus alternans

8. Pulsus alternans occurs in – *(PGI-June 98)*
   A. Constrictive pericarditis
   B. Viral myocarditis
   C. Hypokalemia
   D. MI

### Pulsus Bigeminus

9. All of the following statements about Pulsus Bigeminus are true, except: *(NBE)*
   A. Must be distinguished from Pulsus Alternans
   B. Is a sign of digitalis toxicity
   C. Compensatory pause is absent
   D. Rhythm is Irregular
10. Pulsus Bigeminus is seen in therapy with: *(NBE)*
   A. Digitalis
   B. Beta Blockers
   C. ACE Inhibitors
   D. Calcium Channel Blockers

### Miscellaneous Pulses

11. Water hammer pulse is seen in- *(AIIMS May 07)*
   A. Aortic stenosis
   B. Aortic regurgitation
   C. Aortic stenosis and Aortic regurgitation
   D. Mitral regurgitation
12. Double apical impulse is seen in – *(PGI Dec-98)*
   A. MR
   B. AR
   C. AS
   D. MS

## Jugular Venous Pulse (JVP)

13. All of the following phases of the jugular venous pulse and their causes are correctly matched, *except*:
   A. 'c' wave - onset of atrial systole *(AI 2002)*
   B. 'a-x' descent - atrial relaxation
   C. 'v-y' - emptying of blood from right atrium into right ventricle
   D. 'y-a' ascent - filling of the right atrium from the vena cava
14. Which of the following is the correct statement regarding findings in JVP *(AI 2002)*
   A. Cannon wave : Complete heart block
   B. Slow vy descent : Tricuspid regurgitation
   C. Giant c wave : Tricuspid stenosis
   D. Increased JVP with prominent pulsations : SVC obstruction
15. Giant 'a' waves in JVP occur in *all except:*
   A. Junctional rhythm *(AI 1996)*
   B. Pulmonary hypertension
   C. Tricuspid regurgitation
   D. Complete heart block
16. In the JVP, 'a' waves are absent in : *(AI 1994)*
   A. Atrial fibrillation

B. Mitral stenosis
C. Tricuspid atresia
D. Sick sinus syndrome

17. 'C' wave in JVP is due to- *(AIIMS Nov 07)*
A. Atrial contraction
B. Tricuspid valve bulging into right atrium
C. Right atrial filling
D. Rapid ventricular filling

18. C wave in JVP indicates: *(AI 2009)*
A. Atrial contraction
B. Bulging of tricuspid valve
C. Ventricle systole
D. Rapid ventricular filling

19. Typical JVP finding in cardiac tamponade –
A. Absent 'Y' descent *(PGI-June-2000)*
B. Prominant 'a' wave
C. Absent 'a' wave
D. Prominent 'Y' wave

## Pulse Pressure

20. Pulse pressure is: *(AIIMS May 93)*
A. 1/3 diastolic + 1/2 systolic B.P.
B. 1/2 diastolic + 1/3 systolic B.P.
C. Systolic – diastolic B.P.
D. Diastolic + 1/2 systolic B.P.

21. Wide pulse pressure may be seen in all Except:
A. Aortic Regurgitation *(AI 1991)*
B. PDA
C. Complete Heart Block
D. Congestive Heart failure

22. Wide pulse pressure is seen in all except: *(NBE)*
A. PDA
B. Aortic stenosis
C. Aortic Regurgitation
D. A.V. malformation

## Pulse Deficit

23. Pulse deficit of more than 10 per minute is seen in:
A. Ventricular Premature Contraction (VPC) *(NBE)*
B. Bradyarrhythmias
C. Atrial Fibrillation (AF)
D. Ventricular Fibrillation (VF)

24. Pulse deficit may be seen in all of the following, Except : *(NBE)*
A. Ventricular Premature Contraction (VPC)
B. Bradyarrhythmias
C. Atrial Fibrillation (AF)
D. Tachyarrhythmias

25. All of the following statements about Pulse deficit in Atrial Fibrillation are true , except: *(NBE)*
A. Usually more than 10/minute
B. Increases with faster ventricular rates
C. May be absent in digitalis intoxication
D. Radial pulse rate may be more than ventricular pulse rate

## Cardiac Auscultation: Heart Sounds and Murmurs

### General

26. Erb's Point in cardiology refers to: *(NBE)*
A. Right 2nd intercostal space
B. Left 2nd intercostal space
C. Right 3rd intercostal space
D. Left 2nd intercostal space

27. S2 is best appreciated in: *(NBE)*
A. 3rd left intercostal space
B. 2nd right intercostal space
C. 4th left intercostal space
D. 5 left intercostal space

28. P2 is best appreciated in : *(NBE)*
A. 2nd left intercostal space
B. 2nd right intercostal space
C. 4th left intercostal space
D. 5 left intercostal space

### First Heart Sound (S1)

29. All of the following are true about S1, except:
A. Lower frequency than $S_2$ *(AI 1991)*
B. Caused by closure of mitral valve
C. Heard at the end of ventricular systole
D. Better heard with diaphragm of stethoscope

30. First heart sound is soft in all, *except*:
A. Short PR interval *(AIIMS Dec 95)*
B. Ventricular septal defect
C. Mitral regurgitation
D. Calcified valve

31. Causes of soft S1 include: *(PGI June 97)*
A. Long standing severe MS
B. Obesity
C. Mitral Regurgitation
D. Pleural effusion
E. All of the above

32. All of the above Loud $S_1$ is caused by (select two correct options):
A. Calcified mitral valve. *(PGI Dec 04)*
B. MVP
C. Short Pr interval
D. Tachycardia
E. Dilatation or widening of mitral valve after valvotomy

33. Loud S1 in Mitral stenosis is caused by:
A. Prolonged flow through mitral valve
B. 1st degree heart block *(PGI June 99)*
C. Calcification of the valve
D. Immobilization of valve

34. Reverse splitting of first heart sound in heard in (select two correct options): *(PGI June 04)*
    A. RBBB
    B. LBBB
    C. Tricuspid stenosis
    D. AR
    E. Atrial myxoma

**Second Heart Sound (S2)**

35. Wide split S2 occurs in: *(AIIMS May 93)*
    A. VSD (ventricular septal defect)
    B. Mitral stenosis
    C. ASD (Atrial septal defect)
    D. Coarctation of aorta

36. Paradoxical splitting of second heart sound is seen in? *(NBE)*
    A. RBBB
    B. ASD
    C. LBBB
    D. VSD

37. Wide-split second heart sound is seen in (select two options) – *(PGI Dec 02)*
    A. ASD
    B. LBBB
    C. PDA
    D. MR
    E. PS

38. Wide-splitting of $S_2$ is seen in (select three correct options): *(PGI Dec 06)*
    A. ASD
    B. MR
    C. PDA
    D. PS
    E. LBBB

39. Fixed splitting of S2 may be seen in all except:
    A. Pulmonary embolism *(PGI June 95)*
    B. PS
    C. ASD
    D. LBBB

40. Reverse splitting of S2 is seen in all except (select two options): *(PGI Dec 05)*
    A. LBBB
    B. WPW type A
    C. LV pacing
    D. Systemic hypertension
    E. Post-stenotic dilatation in AS

41. Single second heart sound is seen in (select three options): *(PGI Dec 04)*
    A. TOF
    B. Pulmonary arterial hypertension
    C. Pulmonary atresia
    D. Corrected TGA
    E. Severe pulmonary stenosis

42. Loud pulmonary component of second heart sound heard in (select two options) – *(PGI June 04)*
    A. Pulmonary hypertension
    B. TOF
    C. Eissenmenger's syndrome
    D. Pulmonary stenosis
    E. AS

**Third Heart Sound (S3)**

43. Third heart sound is seen in all *except* :
    A. Athletes *(AIIMS Dec 98)*
    B. Mitral stenosis
    C. Constrictive pericarditis
    D. LVF

44. All of the following statements about third Heart sound (S3) are true, except: *(AI 2010)*
    A. Occurs due to rapid filling of the ventricles during atrial systole
    B. Seen in in Constrictive Pericarditis
    C. Seen in Atrial Septal Defect (ASD)
    D. Seen in Ventricular Septal Defect (VSD)

45. True about third heart sound is – *(PGI Dec-98)*
    A. Absent in Chr. Constrictive pericarditis
    B. Absent in aortic aneurysm
    C. Absent in MS
    D. Normal physiologically in Athletes

**Fourth Heart Sound (S4)**

46. Which of the following is true about fourth heart sound 'S4' : *(AI 07)*
    A. Can be heard by the unaided ear
    B. Frequency is greater than 20 Hz
    C. Heard during ventricular filling phase
    D. Heard during ventricular ejection phase

47. S4 is seen in all of the following, Except:
    A. Thyrotoxicosis *(AIIMS May 94)*
    B. Acute MI
    C. Atrial fibrillation
    D. Hypertrophic cardiomyopathy

48. $S_4$ is not seen in : *(AIIMS May 95)*
    A. Ventricular aneurysm
    B. Mitral regurgitation
    C. Hypertrophic cardiomyopathy
    D. Hypertension

**Added Sound**

49. All of the following heart sounds occur shortly after $S_2$ *except*: *(AI 2003)*
    A. Opening snap
    B. Pericardial knock
    C. Ejection click
    D. Tumor plop

50. Following is true regarding opening snap : *(AIIMS Nov 02)*
A. It is a high-pitched diastolic sound.
B. It s due to opening of stenosed aortic valve.
C. It indicates pulmonary arterial hypertension.
D. It preceedes the aortic component of second heart sound.

51. All of the following sounds are diastolic sounds, Except: *(PGI- Dec-06)*
A. S3
B. S4
C. Opening snap
D. Ejection chick

52. Midsystolic click is characteristic feature of: *(NBE)*
A. MVP
B. MS
C. AR
D. POA

53. Systolic thrill in left 2nd and 3rd intercostals space may be seen in all of the following, Except *(AI 2009)*
A. Subpulmonic VSD
B. Pulmonic stenosis
C. Ebstein's anomaly
D. Pink TOF

## Cardiac Murmur

54. An early systolic murmur may be caused by all of the following except: *(AI 2003)*
A. Small ventricular septal defect
B. Papillary muscle dysfunction
C. Tricuspid regurgitation
D. Aortic stenosis

55. All of the following murmurs may be heard in patients with aortic regurgitation *except* : *(AIIMS Nov 02)*
A. High-pitched decrescendo diastolic murmur.
B. Soft, low pitched mid distolic rumbling murmur.
C. Mid-systolic ejection flow murmur
D. Pansystolic murmur.

56. Mid-diastolic Murmur with presystolic accentuation is typically seen in: *(NBE)*
A. Mitral stenosis
B. Mitral Regurgitation
C. Aortic stenosis
D. MVP

57. Which of the following murmurs increase with Valsalva maneuver?
A. MR *(AIIMS Nov 2010)*
B. VSD
C. AS
D. HOCM

58. A young patient presents with a systolic murmur at the apex. The murmur increases on both handgrip and valsalva maneuver. Which of the following conditions is most likely? *(AI 04)*
A. HOCM
B. AS
C. MVP
D. VSD

59. Which of the following murmurs increase with valsalva maneovre *(AIIMS May 09)*
A. Mitral stenosis
B. HOCM
C. Mitral Regurgitation
D. Aortic stenosis

60. What is false in relation to Carey Coombs Murmur?
A. Delayed Diastolic Murmur *(AIIMS Nov 06)*
B. Seen in Rheumatic Fever
C. Associated with AR
D. Low Pitched Murmur

61. Carey coomb murmur is seen in – *(PGI Dec 97)*
A. Severe mitral stenosis
B. Acute rheumatic carditis
C. Pure aortic regurgitation
D. Severe pulmonary HT

62. Rytand's murmur is seen in *(NBE)*
A. A-V Block
B. Mitral Stenosis
C. Aortic Stenosis
D. Aortic Regurgitation

63. Continuous murmur is found in all, EXCEPT:
A. Mitral stenosis with mitral regurgitation
B. Patent ductus arteriosus *(AIIMS May 93)*
C. Rupture of sinus of Valsalva
D. Systemic arteriovenous (AV) fistula

64. Continuous murmur is seen in all the following *except:* *(AI 1995)*
A. Aortic sinus of valsalva rupture
B. Coarctation of Aorta
C. AV malformations
D. Peripheral pulmonary stenosis

65. A continuous murmur is heard in all of the following conditions except: *(AIIMS May 05)*
A. Ventricular septal defect with aortic regurgitation
B. Patent ductus arteriosus
C. Coronary arteriovenous fistula
D. Venous hum

66. Continuous murmur is present in (select two options)
A. PDA *(PGI June 06)*
B. AS with AR
C. Shunt between pulmonary & subclavian artery
D. VSD with AR

67. Continuous murmur is found in (select three options)
A. AS combined with AR *(PGI Dec 04)*
B. Systemic A V fistula
C. PDA with reversal f shunt
D. Aortopulmonary window
E. Rupture of sinus valsalva

68. A new systolic murmur after Acute myocardial infarction may be due to all of the following Except: *(AIIMS May 1993)*
A. Complete heart block
B. Rupture of Interventricular septum
C. Papillary muscle dysfunction
D. Ischemic cardiomyopathy

## Cardiovascular Clubbing

69. Cardiovascular causes of digital clubbing include all of the following Except: *(NBE)*
A. Infective Endocarditis
B. Arteriovenous Fistulos
C. Tricuspid Atresia
D. Aortic Dissection

## Electrocardiogram and Arrhythmias

### Cardiac Axis

70. Normal Axis of the heart is best described as being between: *(NBE)*
A. – 30 to +90
B. + 30 to -90
C. – 30 to -90
D. +90 to ±180

71. Normal heart axis is: *(NBE)*
A. -90 to + 90°
B. -90 to + 180°
C. -30 to +90°
D. -90 to 180°

72. -30 TO -60 degree axis deviation indicates: *(NBE)*
A. Left Axis Deviation
B. Right Axis Deviation
C. Extreme Right Axis Deviation
D. Normal Cardiac Axis

73. -30 TO -60 degree axis deviation is seen in: *(NBE)*
A. Left Ventricle Hypertrophy
B. Right Ventricle Hypertrophy
C. Left Posterior Fascicular Block
D. Lateral wall Myocardial Infarction

74. Left Axis Deviation is seen as *(NBE)*
A. A. Positive in Lead I and Positive in Lead II
B. B. Positive in Lead I and Negative in Lead II
C. C. Negative in Lead I and Negative in Lead II
D. D. Negative in Lead I and positive in Lead II

### P wave

75. P wave is due to: *(AI 99)*
A. Atrial depolarization
B. Atrial repolarization
C. Ventricular depolarization
D. Ventricular repolarization

76. The normal P wave is inverted in lead : *(NBE)*
A. LI
B. LII
C. aVF
D. aVR

77. The normal P wave is biphasic in lead: *(NBE)*
A. V1
B. LII
C. aVF
D. aVR

78. Absent P Wave is seen in: *(NBE)*
A. Atrial Fibrillation
B. Cor-pulmonale
C. Mitral Stenosis
D. COPD

79. A patient in regular rhythm presents with absent P waves on ECG. Leads II, III and AVF reveal a Saw-Tooth Pattern. Which of the following is the most likely diagnosis: *(NBE)*
A. Atrial Fibrillation
B. Atrial Flutter with Variable Block
C. Atrial Flutter with Fixed Block
D. Multifocal Atrial Tachcardia

80. A wide and notched P wave is typically seen in: *(NBE)*
A. Mitral Stenosis
B. Cor-Pulmonale
C. COPD
D. Pulmonary embolism

### QRS Complex

81. QRS complex indicates- *(AI 98)*
A. Atrial repolarization
B. Atrial depolarization
C. Ventricular repolarization
D. Ventricular depolarization

82. A QRS duration between 100 and 120 milliseconds suggests all of the following, Except: *(NBE)*
A. Normal
B. Left anterior Fascicular Block
C. Left posterior Fascicular Block
D. Left Bundle Branch Block

83. Wide QRS complex ≥ 0.12 seconds may be seen in all of the following EXCEPT: *(NBE)*
A. Hyperkalemia
B. Wolf Parkinson White Syndrome
C. Ventricular Tachycardia
D. Left Anterior Fascicular Block

84. Wide QRS complex is typically seen in *(NBE)*
A. Bundle Branch block
B. Sick sinus sydrome
C. Mobitz Type I block
D. Mobitz Type II block

85. The ECG of a 40 year old male was recorded using standard bipolar limb leads. The sum of voltage of the

three standard leads was found to be 5 millivolts. This indicates: *(AIIMS May 05)*
A. A normal heart
B. Right ventricular hypertrophy
C. Left ventricular hypertrophy
D. Increased cardiac muscle mass

86. Low QRS voltage on ECG indicates: *(NBE)*
A. Pulmonary embolism
B. Pericardial effusion
C. Cor pulmonale
D. Infective endocarditis

87. Low QRS voltage on ECG with left ventricular hypertrophy on Echocardiography suggests a diagnosis of: *(NBE)*
A. Pericardial effusion
B. Cardiac Amyloidosis
C. Corpulmonale
D. Infective endocarditis

88. In LVH, SV1 + RV 6 is more than _____ mm? *(NBE)*
A. 25
B. 30
C. 35
D. 40

## T Wave

89. Tall T waves on ECG are seen in: *(NBE)*
A. Hyperkalemia
B. Hypokalemia
C. Hypercalcemia
D. Hypocalcemia

## ST Segment

90. ST elevation is seen in all of the following conditions *except*: *(AIIMS 2002)*
A. Myocardial infarction
B. Coronary artery spasm
C. Constrictive pericarditis
D. Ventricular aneurysm

91. All of the following may cause ST segment elevation on EKG, except : *(AI 2005)*
A. Early repolarization variant.
B. Constrictive pericarditis.
C. Ventricular aneurysm.
D. Prizmetal angina.

92. What is diagnostic of fresh myocardial infarction in ECG : *(AIIMS May 95)*
A. QT interval prolongation
B. P mitrale
C. ST segment elevation
D. ST segment depression

## QT Interval

93. QT prolongation is seen in all, *except*:
A. Hypothermia *(AIIMS June 2000)*
B. Digitalis toxicity
C. Hypocalcemia
D. Romanowand syndrome

94. QT interval is shortened in- *(AI 95)*
A. Hypocalcaemia
B. Hypokalemia
C. Hypercalcemia
D. Hyperkalemia

95. Hypercalcemia in ECG is diagnosed by:
A. Increased QT interval *(PGI Dec-99)*
B. Decreased QT interval
C. Increased PR interval
D. Tall T waves

96. Hypocalcemia is characterized by all of the following features except- *(AI 03)*
A. Numbness and tingling of circumoral region
B. Hyperactivity tendon reflexes
C. Shortening of Q-T interval in ECG
D. Carpopedal spasm

## Hypo/Hyperkalemia

97. All are ECG changes in hypokalemia, *except*
A. U wave *(AIIMS Dec 97)*
B. ST segment sagging
C. T-wave flattening or inversion
D. QT interval prolongation

98. The following ECG findings are seen in Hypokalemia: *(AI 2007)*
A. Increased PR interval with ST depression
B. Increased PR interval with peaked T wave
C. Prolonged QT interval with T wave inversion
D. Decreased QT interval with ST depression

99. All of the following are the electrocardiographic features of Hyperkalemia, except- *(AIIMS May 04)*
A. Prolonged PR interval
B. Prolonged QT interval
C. Sine wave patterns
D. Loss of P waves

100. All of the following may occur due to hyperkalemia, except : *(AI 06)*
A. Prolonged PR interval
B. Prolonged QRS interval
C. Prolonged QT interval
D. Ventricular asystole

## Digitalis Toxicity

101. All of the following electrocardiographic findings may represent manifestations of digitalis intoxication, *except* *(AIIMS Nov 99)*
A. Bigeminy
B. Junctional tachycardia
C. Atrial flutter
D. Atrial tachycardia with variable block

### Miscellaneous

102. In left sided massive pneumothorax, ECG shows all, except- *(AIIMS May 94)*
   A. Left axis deviation
   B. Absent R wave
   C. Pathological Q waves
   D. Precordial T wave inversion

103. Which of the following ECG changes is least likely in a patient with left pneumothorax : *(AIIMS Nov. 2000)*
   A. Inversion of T wave
   B. Left axis deviation
   C. Small R wave
   D. Electrical alternans

## Arrhythmias

### AF and PSVT

104. Atrial fibrillation may occur in all the following conditions, except- *(AIIMS May 03)*
   A. Mitral stenosis
   B. Hypothyroidism
   C. Dilated cardiomyopathy
   D. Mitral regurgitation

105. Most common in Arrhythmia in ICU Patients is *(NBE)*
   A. Atrial Flutter
   B. Atrial Fibrillation
   C. PSVT
   D. NPAT

106. A chronic alcoholic develops palpitations suddenly after alcohol binge. Which of the following arrythmia is most commonly associated with alcohol binge in the alcoholics? *(AIIMS Nov 01)*
   A. Ventricular fibrillations
   B. Verticular premature contractions
   C. Atrial flutter
   D. Atrial fibrillation

107. All of the following are true about Atrial Fibrillation, Except *(NBE)*
   A. ↑ risk of thromboembolism
   B. digoxin for treatment
   C. anticoagulation not required
   D. aspirin given

108. A person with mitral regurgitation and atrial fibrillation presents with syncope. On examination the person has a heart rate of 55. What is the most probable cause ? *(AI 2007)*
   A. Digitalis toxicity
   B. Incomplete heart block
   C. Stroke
   D. Subarachnoid Haemorrhage

109. In a patient with chronic atrial fibrillation with a regular beat of 60/min, the most probable cause is:
   A. Sleep *(AIIMS May 01)*
   B. Digitalis toxicity
   C. Sino nodal block
   D. Hypothyroidism

110. Drug of choice in PSVT is : *(AI 1998)*
   A. Amiodarone
   B. Lingnocaine
   C. Quinidine
   D. Adenosine

111. Drug of choice for Paroxysmal Supraventricular Tachycardia (PSVT) is: *(NBE)*
   A. Metaprolol
   B. Amiadarane
   C. Adenosine
   D. Lidocaine

112. What is the drug of choice to control supraventricular tachycardia : *(AIIMS Nov. 05)*
   A. Adenosine
   B. Propranolol
   C. Verapamil
   D. Digoxin

113. Drug of choice for maintenance therapy in PSVT IS
   A. Amiodarone *(NBE)*
   B. Lignocaine
   C. Verapamil
   D. Adenosine

### VT, VF and PVCs

114. All of the following features can differentiate between ventricular tachycardia and supraventricular tachycardia *except*: *(AIIMS Nov 98)*
   A. QRs < 0.14 seconds
   B. Ventricular rate > 160/min
   C. Variable first heart sound
   D. Relieved by carotid sinus massage

115. In a patient with wide-complex tachycardia, the presence of all of the following in the ECG indicates ventricular tachycardia except *(AIIMS Nov 03)*
   A. Atrioventricular dissociation
   B. Fusion beats
   C. Typical right bundle branch block
   D. Capture beats

116. Board complex tachycardia, due to ventricular tachycardia is suggested by all except?
   A. Fusion Beats *(NBE)*
   B. AV dissociation
   C. Capture Beats
   D. Termination of tachycardia by carotid Sinus massage

117. Broad complex tachycardia due to ventricular a tachycardia is suggested by (select three correct options): *(PGI –1994)*
   A. Fusion Beats
   B. AV dissociation

C. Capture Beats
D. Termination of tachycardia by carotid massage
E. Triphasic QRS in V1

118. Ventricular Tachycardia is represented by all, Except: *(PGI 1996)*
A. Wide QRS complex
B. AV dissociation
C. Capture Beats
D. Fusion beats
E. Typical RBBB QRS complex

119. Which of the following statements about Premature Ventricular Beats is false: *(PGI 1997)*
A. Sequential depolarization of ventricles
B. Wide, Bizzare, Notched QRS complexes
C. Prevalence decreases with age
D. Palpitations is a common presenting feature

120. All of the following are features of Premature Ventricular Complexes, Except *(AI 1993)*
A. Wide QRS complex
B. Absent P wave
C. Complete compensatory pause
D. Prolonged PR interval

121. Which of the following is the most characteristic EKG finding of ventricular premature beats (select one single best correct option): *(PGI- June-04)*
A. Fusion beat
B. Narrow QRS complex
C. AV Dissociation
D. Wide QRS complex
E. Capture beat

122. All of the following may be seen in ventricular premature beats, Except: *(PGI June 04)*
A. Fusion beat
B. Narrow QRS complex
C. AV Dissociation
D. Wide QRS complex
E. Capture beat

123. Accelerated Idioventricular Rhythm (AIVR) is the most common arrhythmia associated with:
A. Dilated cardiomyopathy *(AI 2010)*
B. Myocardial Reperfusion
C. Digitalis Intoxicatiun
D. Myocarditis

## Torsades De Pointes

124. Feature of Torsade de pointes is: *(AIIMS Dec 97)*
A. Wide QRS complex
B. Short QRS complex
C. Prolonged QTc interval
D. Short QTc interval

125. Congenital long QT syndrome can lead to-
A. Complete heart block *(AIIMS May 2003)*
B. Polymorphic ventricular tachycardia
C. Acute myocardial infarction
D. Recurrent supraventricular tachycardia

126. Torsade-de-pointes is caused by – *(PGI June 99)*
A. Hypermagnesemia
B. Metabolic acidosis
C. Hypomagnesmia
D. Metabolic alkalosis

## WPW Syndrome

127. WPW syndrome is caused by: *(NBE)*
A. Bundle Branch Block
B. Right sided accessory pathway
C. Ectopic pacemaker in atrium
D. Left bundle Branch block

128. The most common accessory pathways leading to WPW syndrome is: *(NBE)*
A. Left free wall
B. Posteroseptal
C. Right free wall
D. Anteroseptal

129. The most common reentrant tachycardia associated with WPW syndrome is *(PGI 2012)*
A. Orthodromic AV reentry
B. Antidromic AV reentry
C. Rapidly conducting AF
D. None

130. All are ECG findings in Wolf Parkinson's white syndrome, *except* : *(AIIMS Feb 97)*
A. Narrow QRS complexes
B. Normal QT interval
C. Slurred and tall QRS
D. Short PR interval

131. All of the following statements about WPW syndrome are true, Except: *(PGI Dec 05)*
A. More common in females
B. Rt ventricular aberrant is commonly seen
C. Incidence ↓ with age
D. Heart is structurally normal
E. Incidence is 0.3 to 0.7%.

132. The drug of choice in patients with Wolff-Parkinson-White syndrome with atrial fibrillation is-
A. Digitalis *(AIIMS Nov 03)*
B. Procainamide
C. Verapamil
D. Adenosine

133. A Patient with short PR interval and Delta waves on ECG presents to the emergency department with Atrial Fibrillation and rapid ventricular rate. He is hemodynamically stable. All of the following agents may be used in the management, except:
A. Verapamil *(AIIMS 2013)*
B. Procainamide
C. Ibutilide
D. Amiodarone

134. Which of the following is the treatment of choice for Atrial Fibrillation in patients with WPW Syndrome who are hemodynamically unstable: *(AIIMS 2013)*

A. Procainamide
B. Digoxin
C. DC Cardioversion
D. Radiofrequency Ablation of the bypass tract

135. Radiofrequency ablation is done for : *(AIIMS June 98)*
A. Ventricular tachycardia
B. PSVT
C. WPW
D. Atrial tachycardia

## Heart block and Conduction Disturbance

136. Sinus Bradycardia is defined as heart rate of? *(NBE)*
A. Less than 40/min
B. Less than 50/min
C. Less than 60/min
D. Less than 70/min

137. All of the following are features of Mobitz Type I block, except: *(AI-1992)*
A. Constant PR interval
B. Normal QRS morphology
C. Regular Atrial Rhythm
D. Atrial rate > ventricular rate

138. Constant PR interval is seen in: *(PGI-1997)*
A. First degree block
B. Second degree – Mobiz type I block
C. Second degree – Mobitz type II block
D. Third degree block

139. Which of the following may be seen in second degree Heart block (select three options): *(PGI Dec 05)*
A. Change in QRS complex morphology
B. Atrial rate more than ventricular rate
C. Prolonged conduction time
D. One P wave to each QRS complex
E. No constant Relationship between P wave and QRS complex

140. True statement regarding Atrioventricular block with atrial tachycardia is : *(AIIMS Nov 98)*
A. Seen in WPW syndrome
B. Is a complication of pacemaker
C. Can occur in normal person occasionally.
D. Seen in Digitalis toxicity with $K^+$ depletion.

141. Most common cause of Acquired Complete Heart Block in children is *(NBE)*
A. Cardiac Surgery
B. Acute Rheumatic Fever
C. Drug Overdose
D. Myocarditis

142. In the treatment of severe bradycardia, all of the following can be the best modality of treatment except:
A. Atropine *(AIIMS Nov. 05)*
B. Pacing
C. Isoproterenol
D. Diltiazem

## Athletic Syndrome

143. ECG features of Athlete's Heart include all of the following except: *(NBE)*
A. High QRS Voltage
B. Early repolarization
C. Tall peaked T waves
D. Shortened QT Interval

144. Which of the following ECG changes in an Asymptomatic Athlete's Heart should be considered pathological? *(NBE)*
A. Increased amplitude of QRS
B. Second Degree (Mobitz 2) heart block
C. Prominent U Waves
D. T Wave inversion

145. Which of the following ECG changes in an Asymptomatic Athlete's Heart should be considered pathological? *(NBE)*
A. Increased amplitude of QRS
B. Second Degree (Mobitz 1) heart block
C. Prolonged QTc Interval
D. T Wave inversion

146. Athletic syndrome is characterized by: *(PGI June 99)*
A. Increased amplitude of QRS
B. Tachycardia
C. Decreased QT interval
D. U-waves

## Congestive Heart Failure and PCWP

147. All the following are features of right sided heart failure, Except: *(AI 2009)*
A. Increased PCWP
B. Pulsatile liver
C. Increased JVP
D. Positive hepatojugular reflex

148. All of the following are true about Right Ventricular Infarcts, Except *(NBE)*
A. Nocturia
B. Hepatomepaly
C. Ascitis
D. Normal JVP

149. Which of the following is not a major Framingham criteria in CHF: *(AIIMS Nov 2008)*
A. Cardiomegaly
B. Paroxysmal nocturnal dyspnea
C. S3 gallop
D. Hepatomegaly

150. Left ventricular Hypertropy is caused by all, Except:
A. M.S (Mitral stenosis) *(AIIMS Nov 09)*
B. A. S (Aortic Stenosis)
C. M.R (Mitral Regurgitation)
D. A. R (Aortic Regurgitation)

151. CCF is associated with increase in all the following except: *(AI 2007)*
A. Right atrial mean pressure

B. Serum Sodium
C. Urea
D. Nor epinephrine

152. Positive hepatojugular reflux is found in conditions except: *(AI 2009)*
A. Tricuspid regurgitation
B. Right heart failure
C. Decreased after load
D. PS

153. Positive Hepatojugular Reflux is found in all of the following conditions, except: *(AIIMS May 2011)*
A. Tricuspid Regurgitation
B. Precapillary Pulmonary Hypertension
C. Right Ventricular Infarction
D. Decreased After-load

154. Enlarged Pulsative liver with ascitis is typically seen in: *(AIIMS May 2011)*
A. Tricuspid Regurgitation (TR)
B. Mitral Regurgitation (MR)
C. Mitral stenosis
D. Pulmonary stenosis (PS)

155. Left atrial filling pressure closely approximates-
A. Pulmonary capillary wedge pressure
B. Central venous pressure *(AIIMS May 93)*
C. Intrapleural pressure
D. Intracranial pressure

156. A Patient comes with sudden respiratory distress. On examination, bilateral basal crepts are present over chest suggestive of pulmonary edema. Alveolar wedge pressure is normal. The likely cause is-
A. Narcotic overdose *(AIIMS June 2000)*
B. Congestive heart failure
C. Myocardial infarction
D. Cardiogenic shock

157. Normal PCWP with pulmonary oedema is seen in-
A. Left atrial myxoma *(AIIMS June 98)*
B. High altitude
C. Pulmonary vein obstruction
D. Pulmonary artery obstruction.

158. Pulmonary edema associated with normal PCWP is observed. Which of these is not a cause: *(AI 01)*
A. High altitude
B. Cocaine overdose
C. Post cardiopulmonary bypass
D. Bilateral renal artery stenosis

159. A 45-year-old woman underwent a modified radical mastectomy 4 years ago. She was treated for multiple bone metastases with cyclophosphamide, doxorubicin, and fluorouracil for 6 months. She is complaining of exertion on exercise, swelling of the legs, and swelling around eyes in the morning. On examination, she has bilateral rales in the lungs, S1, S2 audible, S3, S4 gallop present. Her BP is 149/117 mm Hg, PR is 80/min, and RR is 18/min. What is the most likely cause for her cardiac condition?
A. Systolic dysfunction CHF *(AIIMS May 06)*
B. Drug induced cardiac toxicity
C. Metastatic cardiac disease
D. Pneumonia

160. Assays of which of the following biomarkers is most commonly used in the diagnosis of Heart failure
A. Brain Natriuretic Peptide (BNP) *(NBE)*
B. Atrial Natriuretic Peptide (ANP)
C. Endothelin- 1 (ET-1)
D. Adrenomedullin

161. Which of the following biomarkers has been shown to correlate best with pulmonary vascular resistance in patients with heart failure: *(NBE)*
A. Brain Natriuretic Peptide (BNP)
B. Atrial Natriuretic Peptide (ANP)
C. Endothelin- 1 (ET-1)
D. Endothelin- 2 (ET-2)

162. Which of the following biomarkers is released from ventricular myocytes: *(NBE)*
A. Brain Natriuretic Peptide (BNP)
B. Atrial Natriuretic Peptide (ANP)
C. Endothelin1
D. Endothelin2

163. All of the following are used in the initial management of acute life threatening cardiogenic pulmonary edema, except: *(AI 2012)*
A. Digoxin
B. Morphine
C. Furosemide
D. Positive Pressure Ventilation

164. All of the following medications may be used in congestive cardiac failure, Except *(AIIMS Nov 09)*
A. Spironolactone
B. Nitrates
C. Nesiritide
D. Trimetazidine

165. All of the following are true about starting beta-blocker therapy in cases of CHF, Except *(NBE)*
A. They should be initiated at the effective doses
B. They should be gradually increased over weeks
C. Special precautions should be taken in NYHA class III & IV
D. Carvedilol and Metoprolol are the preferred drugs

166. Treatment of choice for patients with Congestive Heart Failure and an ejection fraction of < 40 percent is: *(NBE)*
A. ACE + Beta Blocker
B. ACE-I + Diuretic
C. ACE-I+ ARB
D. ACE-I + CCB

167. All of the following medications have shown to lower mortality in patients with CHF, Except:
A. ACE – Inhibitors *(NBE)*
B. Beta Blockers
C. Calcium Channel blockers
D. D. Spironolactone

168. In a patient with chronic congestive cardiac failure, all of the following drugs prolong survival *except :*
A. Metoprolol *(AIIMS May 04)*
B. Carvedilol
C. Enalapril
D. Digoxin

169. All of the following statements about digitalis are true *except* : *(AI 1997)*
A. Excretion is mainly renal
B. Oral absorption is good
C. Actively metabolized in liver
D. Lipid soluble

170. Digoxin toxicity is enhanced by all, *except*:
A. Quinidine *(AIIMS Dec 97)*
B. Hypokalemia
C. Hypomagnesemia
D. Hepatic dysfunction

171. All of the following may precipitate digitalis toxicity *except* : *(AI 1997)*
A. Hypocalcemia
B. Hypokalemia
C. Hypomagnecemia
D. Hypothyroidism

172. Treatment of digoxin over dose includes administration of all of the following *except* :
A. Potassium *(AI 1997)*
B. Lignocaine
C. Phenyton
D. Hemodialysis

173. Following are used in treatment of digitalis toxicity except- *(AI 95)*
A. Potassium
B. Lignocaine
C. Fabparticles
D. Hemodialysis

174. All the following are radiological features of Chronic Cor pulmonale *except :* *(AI 1996)*
A. Kerley B lines
B. Prominent lower lobe vessels
C. Pleural effusion
D. Cardiomegaly

## Vulvar Heart Disease

### Mitral Stenosis

175. Area of mitral orifice in adults is: *(AIIMS Dec 94)*
A. 6-8 $cm^2$
B. .5-2 $cm^2$
C. 4-6 $cm^2$
D. 1-4 $cm^2$

176. Mitral stenosis is associated with : *(AI 1997)*
A. Right ventricular hypertrophy
B. Left ventricular hypertrophy
C. Left axis deviation
D. QRS complex

177. Mid diastolic Murmur with presystolic accentuation is typically seen in: *(NBE)*
A. Mitral stenosis
B. Mitral Regurgitation
C. Aortic stenosis
D. MVP

178. All of the following may be seen as severity of mitral stenosis increases Except *(NBE)*
A. Pulsatile liver
B. Atrial fibrillation
C. Opening snap delayed from S2
D. Length of murmur is prolonged

179. Severity of mitral stenosis is assessed by:
A. Loud opening snap *(AI 1998)*
B. Length of murmur *(AIIMS May 03)*
C. Loud $S_1$
D. Splitting $S_2$

180. Severity of mitral stenosis is assessed by (select two options): *(PGI June 02)*
A. Loud $S_1$
B. $S_2$-OS gap
C. Prolonged diastolic murmur
D. $S_3$
E. $S_4$

181. Which clinical sign is suggestive of elevated pulmonary wedge presure in mitral stenosis?
A. Loud OS *(NBE)*
B. Loud S1
C. Mid-diastolic murmur
D. Short A2 –OS interval

182. Double Density sign in Mitral Stenosis is a sign of enlargement of: *(NBE)*
A. Right Atrium
B. Left Atrium
C. Left Auricle
D. Right Auricle

### Mitral Regurgitation

183. Severity of Mitral Regurgitation may be judged by
A. Intensity of murmur *(NBE)*
B. Duration of murmur
C. Left ventricular $S_3$
D. Loud $S_1$

184. The severity of mitral regurgitation is decided by all of the following clinical findings *except*:
A. Presence of mid-diastolic murmur across mitral valve. *(AIIMS May 03)*
B. Wide split second heart sound.
C. Presence of left ventricular S3 gallop.
D. Intensity of systolic murmur across mitral valve

185. A 59 year old man with severe myxomatous mitral regurgitation is asymptomatic, with a left ventricular ejection fraction of 45% and an endsystolic diameter index of 2.9 cm/m2. The most appropriate treatment is: *(AI 2005)*
   A. Mitral valve repair or replacement
   B. No treatment
   C. ACE inhibitor therapy
   D. Digoxin and diuretic therapy

**Mitral Valve Prolapse (MVP)**

186. A young asymptomatic female is observed to have a Midsystolic Click on routine examination. Valves are likely to show *(AI 2010)*
   A. Myxomatous degeneration
   B. Aschoff bodies
   C. Calcific degeneration
   D. Ruptured chordae tendinae
187. All of the following statements about mitral valve prolapse are true except: *(AIIMS Nov 93)*
   A. It is more common in females
   B. Most patients are symptomatic
   C. It has a benign clinical course
   D. Transient cerebral ischemic is a know complication
188. True regarding Mitral valve prolapse syndrome is all, EXCEPT- *(AIIMS Nov 93)*
   A. More common in female
   B. Mostly symptomatic
   C. High incidence of arrhythmia
   D. Transient cerebral ischemia can occur
189. All of the following are true for mitral valve prolapse, except- *(AI 06)*
   A. Transmission may be as an autosomal dominant trait
   B. Majority of the case present with features of mitral regurgitation
   C. The valve leaflets characteristically show myxomatous
   D. The disease is one of the common cardiovascular manifestations of Marfan's Syndrome
190. A 26 yr old asymptomatic woman is found to have arrthymias and a systolic murmur associated with midsystolic clicks; which investigation would you use: *(AI 2001)*
   A. Electrophysiological testing
   B. Tc scan
   C. Echocardiography
   D. Angiography
191. A female patient Chandani develops chest pain which is not associated with exercise and chest auscultation shows multiple non ejection clicks. The investigation which is used to diagnose the disease is :
   A. Echocardiography *(AIIMS June 99)*
   B. Pyrophosphate scan
   C. Thallium 201 scan
   D. ECG

**Aortic Stenosis**

192. Angina pectoris and Syncope are most likely to be associated with: *(AI 1994)*
   A. Mitral stenosis
   B. Aortic stenosis
   C. Mitral regurgitation
   D. Tricuspid stenosis
193. A 63 year old man present with a triad of angina, syncope and congestive heart failure. Which of the following valvular heart lesion can be suspected :
   A. Mitral stenosis *(AIIMS Nov. 05)*
   B. Tricuspid regurgitation
   C. Aortic stenosis
   D. Aortic regurgitation
194. Which of the following valvular heart diseases is most commonly associated with sudden death: *(NBE)*
   A. Aortic Stenosis
   B. Mitral Stenosis
   C. Mitral Regurgitation
   D. Aortic Regurgitation
195. In severe aortic stenosis true finding is :
   A. Late systolic ejection click. *(AIIMS Nov 98)*
   B. Heaving with outward apex
   C. ST segment changes in ECG
   D. Loud $S_2$
196. Which of the following physical signs is seen in a patient with severe aortic stenosis: *(AIIMS 2002)*
   A. Opening snap
   B. Diastolic rumble
   C. Holosystolic murmur
   D. Delayed peak of systolic murmur
197. Exercise testing is absolutely contraindicated in which one of the following: *(AI 2003)*
   A. One week following myocardial infarction
   B. Unstable angina
   C. Aortic stenosis
   D. Peripheral vascular disease
198. Calcification of the aortic valve is seen in :
   A. Aortic stenosis *(AI 95)*
   B. Aortic regurgitation
   C. Marfan's syndrome
   D. Hurler's syndrome
199. A 50-year-old asymptomatic man with established aortic stenosis undergoes Exercise Stress testing according to Bruce Protocol. The stress test was terminated at 11 minutes due to development of fatigue and dyspnea. Regional pressure gradient was observed to be 60 mm Hg between the two sides of the aortic valve. What is the best management.
   A. Angiogram *(AIIMS Nov 2011)*
   B. Aortic valve replacement
   C. Aortic Balooning
   D. Observation

200. Sub-valvular Aortic Stenosis is known to be associated with all of the following, except: *(NBE)*
   A. Aortic Regurgitation
   B. Coarctation of Aorta
   C. Tricuspid Valve Atresia
   D. Ventricular Septal Defect

201. The most common complication of Sub-valvular Aortic Stenosis is: *(NBE)*
   A. Aortic Regurgitation
   B. Mitral Regurgitation
   C. Tricuspid regurgitation
   D. Pulmonary Regurgitation

## Aortic Regurgitation

202. Acute Aortic regurgitation is seen in all the following *except:* *(AI 1994)*
   A. Marfan's syndrome
   B. Acute myocardial infarction
   C. Bacterial endocarditis
   D. Ankylosing spondylitis

203. Aortic regurgitation does NOT occur in :
   A. Acute MI *(AIIMS Sept 96)*
   B. Marfan's syndrome
   C. Rheumatic heart disease
   D. Infective endocarditis

204. All of the following murmurs may be heard in patients with aortic regurgitation *except* : *(AIIMS Nov 02)*
   A. High-pitched decrescendo diastolic murmur.
   B. Soft, low pitched mid distolic rumbling murmur.
   C. Mid-systolic ejection flow murmur
   D. Pansystolic murmur.

205. A 35 year old athlete has height 184 cm., arm span 194 cm., pulse rate 64/min., BP 148/64 mm Hg. Chest auscultation reveals long diastolic murmur over right 2nd intercostal space on routine examination. The probable diagnosis is : *(AIIMS June 99)*
   A. Aortic regurgitation
   B. Atrial septal defect
   C. Ebstein anomaly
   D. Coarctation of aorta

206. A young basketball player with ht 188 cm and arm span 197 cm has a diastolic murmur best heard in second right intercostal space: likely cause of murmur is: *(AI 2001)*
   A. AS
   B. Coarctation of aorta
   C. AR
   D. MR

207. Duroziez's sign is seen in *(NBE)*
   A. Aortic Regurgitation
   B. Tricuspid Regurgitation
   C. Mitral Stenosis
   D. Pericardial effusion

208. LVH is commonly seen with : *(AI 1999)*
   A. Pure mitral stenosis
   B. ASD with fossa-ovalis
   C. Aortic incompetance
   D. Carcinoid syndrome

## Pulmonic Stenosis

209. Obstruction in pulmonary stenosis may occur at the following sites : *(AI 97)*
   A. Supravalvular
   B. Valvular
   C. Subvalvular
   D. All of the above

210. Peripheral pulmonic stenosis is associated with (select two options): *(PGI June 02)*
   A. Subaortic stenosis
   B. Takayasu's arteritis
   C. William syndrome
   D. Coarctation of syndrome
   E. Rubella

211. In pulmonary stenosis the interval between first heart sound (S1) and Systolic ejection click: *(NBE)*
   A. Increases as the severity of PS increases
   B. Decreases as the severity of PS increases
   C. Remains unchanged
   D. Any of the above

## Tricuspid Regurgitation

212. The most common cause of tricuspid regurgitation is secondary to – *(AI-03)*
   A. Rheumatoid heart disease
   B. Dilatation of right ventricle
   C. Coronary artery disease
   D. Endocarditis due to intravenous drug abuse

213. Hepatomegaly with liver pulsation indicates:
   A. TR *(AI 2009)*
   B. MR
   C. Pulmonary hypertension
   D. MS

214. Vitum's Sign is seen in *(NBE)*
   A. Tricuspid Regurgitation
   B. Mitral Stenosis
   C. Aortic Stenosis
   D. Aortic Regurgitation

215. Carvallo's sign is seen in *(NBE)*
   A. Tricuspid Regurgitation
   B. Mitral Stenosis
   C. Aortic Stenosis
   D. Aortic Regurgitation

216. Carvallo's Sign representing a Diastolic Murmur that increases on inspiration is seen in *(NBE)*
   A. Tricuspid Stenosis
   B. Tricuspid Regurgitation
   C. Mitral Stenosis
   D. Aortic Regurgitation

## Ischemic Heart Disease and Atherosclerosis

### Risk Factors / Atherosclerosis:

217. All of the following are risk factors for atherosclerosis except : *(AI 06)*
   A. Increased waist - hip ratio
   B. Hyperhomocysteinemia
   C. Decreased fibrinogen levels
   D. Decreased HDL levels

218. Best predictor for future risk of cardiovascular events, amongst the following is: *(AI 2009)*
   A. hs CRP
   B. Lipoprotein 'a'
   C. Homocysteine
   D. Interleukin 6

219. Which of the following is the best marker to predict future cardiac events *(DNB June 2012)*
   A. hs CRP
   B. Homocystine
   C. Interleuken-6

220. The amino acid which is associated with atherosclerosis is : *(AIIMS May 2006)*
   A. Lysine
   B. Homocysteine
   C. Cysteine
   D. Alanine

221. The risk of coronary artery disease is associated with an elevated level of *(NBE)*
   A. Cysteine.
   B. Cystine.
   C. Homocysteine.
   D. Selenocysteine.

222. The protein which has structural homology with plasminogen and is responsible for myocardial infarction and stroke *(NBE)*
   A. HDL
   B. LP(a)
   C. LDL
   D. Homocysteine

223. Risk factors for coronary artery disease (CAD) (select two options)– *(PGI June 01)*
   A. High HDL
   B. Low LDL
   C. Increased homocysteine levels
   D. Decreased fibrinogen levels
   E. Increased lipoproeins

224. Predisposing factors for coronary artery disease include, all Except: *(PGI Dec 02)*
   A. Homocysteinemia
   B. ↑ Lipoprotein B
   C. ↑ Fibrinogen
   D. ↑ plasminogen activator inhibitors 1

225. Raised serum level of lipoprotein-(a) is a predictor of
   A. Cirrhosis of liver *(AI 03)*
   B. Rheumatic arthritis
   C. Atherosclerosis
   D. Cervical cancer

226. Which of the following increases the susceptibility to coronary artery disease : *(AI 03)*
   A. Type V hyperlipoproteinaemia
   B. Von willebrands disease
   C. Nephrotic syndrome
   D. Systemic lupus erythematosus

227. In an old patient, the best indicator of probability of developing cardiovascular disease can be calculated by- *(AIIMS May 02)*
   A. LDL/HDL ratio.
   B. Triglycerides
   C. Total cholesterol
   D. Serum LDL

228. Most important predictor of coronary artery disease is: *(AIIMS May 09)*
   A. VLDL
   B. LDL
   C. Chylomicron
   D. LDL/HDL

229. An association of which of the following bacteria has been suggested with atherosclerosis: *(NBE)*
   A. Staphylococcus Aureus
   B. Streptococcus Pneumoniae
   C. Chlamydia Pneumoniae
   D. Aspergillus Fumigatus

230. The most important modifiable risk factor for atherosclerosis is: *(NBE)*
   A. Hyperlipidemia
   B. Diabetes mellitus
   C. Cigarette Smoking
   D. Hypertension

231. According to the ATP III Classification Desired levels of total cholesterol is: *(NBE)*
   A. < 250
   B. <200
   C. <100
   D. <40

232. All of the following dietary goals are recommended for patients with high risk of coronary heart disease, Except: *(AI 2011)*
   A. LDL cholesterol < 100 mg/dl
   B. Saturated fat < 7 % of total calories
   C. Salt restriction < 6 gm/day
   D. Avoid Alcohol

233. Which of the following dietary interventions has shown to reduces mortality in patients with coronary heart disease.- *(AIIMS May 07)*
   A. High Fibre diet
   B. Steral Esters
   C. Potassium supplements
   D. Omega 3 polysaturated fatty acids

234. A patient with hypertriglycerdemia is treated with Omega -3- polyunsaturated fatty acids. Treatment with omega-3- polyunsaturated fatty acids, will have the following effect on lipid profile: *(AIIMS Nov 2006)*
   A. Increased LDL and Increased total cholesterol
   B. Decreased LDL and Decreased total cholesterol
   C. Increased LDL and Decreased total cholesterol
   D. Decreased LDL and Increased total cholesterol

235. Which of the following statements about Atherosclerosis is true: *(AIIMS May 2011)*
   A. Intake of Unsaturated Fatty Acids is associated with decreased risk
   B. Extent of lesions in veins is similar as that in arteries
   C. Thoracic Aorta is more commonly involved than abdominal aorta
   D. Hypercholesterolemia alone does not increase the risk of atherosclerosis per se

## Myocardial Infarction / Angina

236. WHO Rose Questionnaire is used for *(NBE)*
   A. Alcohol Addiction
   B. Angina Assessment
   C. DVT Assessment
   D. Arrhythmia Assessment

237. All of the following statements about Universal Definition of Myocardial Infarction are true, Except: *(AIIMS Nov 2011)*
   A. Sudden, unexpected Cardiac death with symptoms of Ischemia.
   B. Elevation of cardiac biomarkers with new regional wall motion abnormality
   C. Three times increase in Troponin levels after Percutaneous Coronary Intervention (PCI)
   D. Three times increase in Troponin levels after Coronary Artery Bypass Grafting (CABG)

238. Most common site of myocardial infraction is:
   A. Anterior wall of left ventricle *(AI 98)*
   B. Posterior wall of left ventricle
   C. Posterior wall of right ventricle
   D. Inferior wall of left ventricle

239. The most common site for myocardial infarction is :
   A. Left atrium *(AI 96)*
   B. Left ventricle
   C. Right atrium
   D. Right ventricle

240. The most common site of Myocardial infarction is:
   A. Anterior wall *(AI 94)*
   B. Interventricular septum
   C. Posterior wall
   D. Inferior wall

241. All of the following arteries are common sites of occlusion by a *except* *(AIIMS May 2005)*
   A. Left anterior descending
   B. Right coronary artery
   C. Circumflex coronary artery
   D. Marginal artery

242. Which of the following ECG findings is associated with acute myocardial Infarction *(NBE)*
   A. Elevation of S wave
   B. Prolonged QT interval
   C. Tall T waves with increased amplitude
   D. Prolonged PR interval

243. ECG is poor in detecting ischemia in areas supplied by which of the following vessels: *(AI 2011)*
   A. Left Anterior Descending (LAD)
   B. Left Circumflex (LCx)
   C. Left Coronary Artery (LCA)
   D. Right Coronary Artery (RCA)

244. Which of the following ECG leads is most sensitive in detecting intraoperative myocardial ischemia *(NBE)*
   A. Lead I
   B. Lead II
   C. Lead $V_1$
   D. Lead $V_2$
   E. Lead $V_5$

245. Wellen's syndrome suggests: *(NBE)*
   A. Stable angina
   B. Unstable angina
   C. Prinzmetal angina
   D. Ludwig angina

246. A 60 year old man presents with chest pain with last 6 hours and is diagnosed as acute myocardial infarction. Angiography showed involvement of anterior descending branch of left coronary artery. The most probable site of infarct is : *(AIIMS May 01)*
   A. Anterolateral wall
   B. Posterior wall
   C. Inferior wall
   D. Septal

247. A 70 year old male patient presented to the emergency department with pain in epigastrium and difficulty in breathing for 6 hours. On examination, his heart rate was chest examination was normal. The patient has been taking omeprazole for gastresophageal reflux disease for last 6 months. What should be the intial investigation :
   A. An ECG *(AIIMS Nov. 05)*
   B. An upper GI endoscopy
   C. Urgent ultrasound of the abdomen
   D. An x-ray chest

248. In stable angina : *(AIIMS Nov 03)*
   A. CK-MB is elevated
   B. Troponin I is elevated
   C. Myoglobin is elevated
   D. The levels of cardiac markers remain unchanged.

249. What is diagnostic of fresh myocardial infarction in ECG: *(AIIMS May 95)*
   A. QT interval prolongation

B. P mitrale
C. ST segment elevation
D. ST segment depression

250. ST elevation and hyperacute T waves in precordeal leads V1 to V6 and in lead aVL indicates:
A. Anterolateral wall MI *(PGI Dec 2000)*
B. Posterior wall MI
C. Inferior MI
D. Lateral wall MI

251. Cardiac Biomarker of Choice for diagnosis of Myocardial Infarction 10 days after the initial event:
A. Troponins *(NBE)*
B. CK-MB
C. Myoglobin
D. LDH

252. Cardiac Biomarker of Choice for diagnosis of Re-infarction 8 days after the initial ischemic event is:
A. Troponins *(NBE)*
B. CK-MB
C. Myoglobin
D. LDH

253. In MI, which enzyme is raised in 4 to 6 hrs. & decreases in 3 to 4 days : *(AIIMS Nov. 2000)*
A. SGOT *(AIIMS June 98)*
B. LDH
C. CPK
D. SGPT

254. A patient presents 12 hours following a Myocardial infarction. Test of choice : *(AIIMS June 98)*
A. Lactate dehydrogenase
B. Cardiac troponins
C. Creatinine phosphokinase
D. Myoglobin

255. Troponin - T is a marker of : *(AIIMS May 2004)*
A. Renal disease
B. Muscular disease
C. Cirrhosis of liver
D. Myocardial infarction

256. Troponin-T is preferable to CPK-MB in the diagnosis of acute myocardial infarction (MI) in all of the following situations except: *(AI 2003)*
A. Bedside diagnosis of MI
B. Postoperatively (after CABG)
C. Reinfarction after 4 days
D. Small infarcts

257. Which of the following is the preferred marker for detecting Acute STEMI in Atheletes: *(AI 2012)*
A. CK-MB
B. Troponin T/I
C. C-Reactive Protein
D. LDH

258. Reperfusion is believed to restore contractile function of: *(AIIMS May 2011)*
A. Stunned Myocardium
B. Hibernating Myocardium
C. Ischemic non-viable myocardium
D. Non ischemic viable myocardium

259. Agent of first choice in an acute attack of Prinzmetal's angina is: *(AI 1995)*
A. Diltiazem
B. Nitrates
C. Propranolol
D. Verapamil

260. The best possible intervention for acute myocardial infarction is: *(AIIMS May 2005)*
A. Streptokinase
B. Streptokinase and aspirin
C. Early primary coronary intervention
D. Streptokinase and heparin

261. Dose of streptokinase to be used in MI is?
A. 0.15 Million units *(NBE)*
B. 1.5 Million units
C. 15 Million units
D. 150 Million units

262. Dose of Reteplase for management of Acute MI is?
A. 5 IU *(NBE)*
B. 10 IU
C. 15 IU
D. 50 IU

263. Half-life of alteplase? *(NBE)*
A. 3 min
B. 6 min
C. 9 min
D. 12 min

264. 40 year old male patient presents to the Emergency department with central chest pain for 2 hours. The ECG shows ST segment depression and cardiac troponins are elevated. Patient has a positive history of previous PCI 3 months back. He is administered Aspirin, Clopidogrel, Nitrates and LMWH, in the Emergency Department and shifted to the coronary are unit. The best recommended course of further action should include *(NBE)*
A. Immediate Revascularization with Thrombolytics
B. Early Revascularization with PCI
C. Continue conservative management and monitoring of cardiac enzymes and ECG
D. Continue conservation management and plan for delayed Revascularization procedure after patient is discharged

265. A 50 year old man with a history of smoking, hypertension, and chronic exertional angina develops several daily episodes of chest pain at rest compatible with cardiac ischemia. The patient is hospitalized. All the following would be part of an appropriate management plan *except* : *(AIIMS Nov 99)*
A. Intravenous heparin
B. Aspirin
C. Intravenous nitroglycerin
D. Lidocaine by bolus infusion

266. The treatment of choice for a patient of Acute ST Elevation Myocardial infarction with cardiogenic shock is: *(NBE)*
   A. Intra-aortic balloon pump (IABP) and PCI
   B. PCI with Angioplasty
   C. Thrombolysis
   D. Intraaortic baloon pump (IABP)

267. A patient present with acute anterior wall infarction and hyotension. Which will be the immediate treatment modality for this atient : *(AI 2007)*
   A. Intra aortic balloon counter pulsation
   B. Anticoagulation
   C. Thrombolytic therapy
   D. Primary antioplasty

268. A patient presents with intense chestpain of 2 hrs duration. ECG shows ST depression in leads I and V1 to V4. There is associated T inversion and CPK-MB is elevated. All of the following should be included in the management of this patient, Except:
   A. Nitroglycerine drip *(PGI June 2000)*
   B. Aspirin
   C. Coronary angiography
   D. Streptokinase
   E. I.V. metoprolol

269. A 40 years old male, chronic smoker comes with acute epigastric discomfort, for past one hour. ECG showing ST segment elevation in inferior leads. What is the immediate intervention? *(AIIMS Nov 07)*
   A. Aspirin
   B. Thrombolytic therapy
   C. IV pantoprazole
   D. Beta blockers

270. All of the following drugs are used in the management of acute myocardial infarction, *except*:
   A. Tissue Plasminogen activator
   B. Intravenous beta blockers
   C. Acetylsalicylic acid *(AIIMS May 04)*
   D. Calcium channel blockers

271. In MI following are used Except: *(PGI Dec 97)*
   A. Fibrinolytics
   B. Plasminogen activator inhibitor
   C. Anti thrombin
   D. Platelet inhibitor

272. Allof the following are used in the management of acute myocardial infarction Except: *(PGI Dec 01)*
   A. Aspirin
   B. Heparin
   C. Alteplase
   D. Warfarin

273. Streptokinase and Urokinase are contraindicated in:
   A. Intracranial malignancy *(AI 2010)*
   B. Pulmonary Embolism
   C. AV fistula
   D. Thrombophlebitis

274. All of the following are complications of streptokinase, Except: *(PGI June 01)*
   A. Joint pain
   B. Inctracranial bleed
   C. Fever
   D. Anaphylaxis
   E. Hypotension

275. A patient with acute inferior wall myocardial infarction has developed shock. Which of the following is the most likely cause of shock
   A. Cardiac rupture *(AIIMS May 04)*
   B. Interventricular septal perforation
   C. Papillary muscle rupture
   D. Right ventricular infarction

276. A previously healthy 58 years old man is admitted to the hospital because of an acute inferior myocardial infarction. Within several hours, he becomes oliguric and hypotensive (blood pressure is 90/60 mmHg). Insertion of a pulmonary artery (Swan-Ganz) catheter reveals the following pressures: pulmonary capillary wedge-4 mm Hg; pulmonary artery- 22/4 mmHg: and mean right atrial- 11 mmHg. This man would best be treated with : *(AIIMS Nov 99)*
   A. Fluids
   B. Digoxin
   C. Dopamine
   D. Intraaortic balloon counter pulsation

277. In a pt of acute inferior wall MI; best modalitiy of rx is: *(AI 2001)*
   A. IV fluids
   B. Digoxin
   C. Diuretics
   D. Vasodilators

278. A patient had an inferior wall myocardial infarction and was in shock. The reason for the patient being in shock is:- *(AIIMS May 02)*
   A. Mitral regurgitation
   B. Infarction causing septal defect
   C. Right ventricular infarction
   D. Decreased ejection fraction from left ventricle

279. In a patient with myocardial infarction the valvular lesion commonly seen in:- *(AIIMS May 02)*
   A. Aortic stenosis
   B. Mitral regurgitation
   C. Aortic regurgitation
   D. Septal defect

280. Ramkumar a 70 year old hypertensive male was admitted in the intensive care unit with transmural anterolateral myocardial infraction. His condition was stable till fifth day of admission, when he developed a pericardial friction rub and pleuritic chest pain which persisted despite narcotic and steroid therapy. On the seventh morning, he suddenly developed marked hypotension. On examination there was marked distension of the jugular veins, accompanied with

electromechanical dissociation. Most likely, the patient had developed : *(AIIMS Nov 02)*
A. Severe acute mitral regurgitation.
B. Ventricular septal rupture.
C. Right ventricular infarction.
D. External cardiac rupture.

281. A new systolic murmur after Acute myocardial infarction may be due to all of the following Except:
A. Complete heart block *(AIIMS May 1993)*
B. Rupture of Interventricular septum
C. Papillary muscle dysfunction
D. Ischemic cardiomyopathy

282. True about Dressler's syndrome is all, except :
A. Occurs with in hours after myocardial infarction
B. Recurrence may be seen
C. Chest pain is common *(AIIMS June 98)*
D. Responds well to salicylates

283. Which is incorrect about Dressler syndrome?
A. Post MI pericarditis *(NBE)*
B. Post MI pleuritis
C. Autoimmune
D. Treatment with steroids is necessary

284. Which of the following tests is used to detect reversible myocardial ischemia *(AIIMS May 09)*
A. Angiography
B. Thallium scan
C. MUGA
D. Resting Echocardiography

285. Which test is performed to detect reversible myocardial ischemia? *(AIIMS May 03)*
A. Coronary angiography.
B. MUGA scan.
C. Thallium scan.
D. Resting echocardiography.

286. Which of the following drugs has been linked with increased cardiac mortality: *(AI 2012)*
A. Rofecoxib
B. Metoprolol
C. Losartan
D. Nicorandil

287. Following an attack of myocardial infarction the mortality and morbidity of the patient is indicated by
A. Ventricular extra systole *(AIIMS June 2000)*
B. Left ventricular ejection fraction
C. Duration of syncope
D. Percentage of narrowness of coronary artery

## Cardiomyopathy/HOCM

288. Cardiomyopathy may be seen in all of the following except : *(AIIMS May 2006)*
A. Duchene muscular dystrophy
B. Friedrich's ataxia
C. Type II glycogen storage disease
D. Alkaptonuria

289. Contractile Dysfunction is the dominant feature of which of the following types of cardiomyopathies
A. Dilated cardiomyopathy *(NBE)*
B. Restrictive cardiomyopathy
C. Hypertrophic cardiomyopathy
D. Infiltrative cardiomyopathy

290. The most common type of cardiomyopathy in India is: *(NBE)*
A. Dilated Cardiomyopathy
B. Hypertrophic Cardiomyopathy
C. Toxic Cardiomyopathy
D. Restrictive Cardiomyopathy

291. The most common toxin causing Dilated Cardiomyopathy is: *(NBE)*
A. Alcohol
B. Chemotherapeutic agents
C. Heavy metal
D. Occupational exposure

292. Tako-Tsubo Cardiomyopathy is a type of: *(NBE)*
A. Dilated Cardiomyopathy
B. Restrictive Cardiomyopathy
C. Hypertrophic Cardiomyopathy
D. Toxic Cardiomyopathy

293. Which one of the following is the most common cause for 'Restrictive cardiomyopathy' :
A. Alcohol *(AIIMS May 04)*
B. Hemochromatosis
C. Amyloidosis
D. Sarcoidosis

294. Which of the following heart diseases is most commonly cause of sudden death in young Athletes: *(NBE)*
A. Aortic Stenosis
B. Mitral Regurgitation
C. Aortic Regurgitation
D. HOCM

295. A 25 years old basket ball player suddenly collapsed while undergoing an athletic event and died. At autopsy the septum was hypertrophied. The most probable diagnosis is- *(AIPGMEE 08)*
A. HOCM
B. Right ventricular conduction Abnormality
C. Epilepsy
D. Snake bite

296. A 26 year old man died suddenly during sporting activity. At autopsy the heart revealed chamber and septum Hypertrophy. The most likely diagnosis is
A. HOCM *(AIIMS May 09)*
B. DCM
C. Arrhythmogenic cardiac problem
D. Restrictive cardiomyopathy

297. All are true about Hypertrophic Obstructive Cardiomyopathy, *except* : *(AI 2000)*
A. β agonist are useful
B. Asymmetrical hypertrophy of septum

C. Dynamic L.V. outflow obstruction
D. Condition improves on passive leg raising

298. Features of Hypertrophic Cardiomyopathy include all of the following except: *(NBE)*
A. Asymmetric Septal Hypertrophy
B. Systolic Anterior Motion of Mitral Valve
C. Dynamic Left Ventricular Outflow Obstruction
D. Pathophysiological Systolic Dysfunction

299. A 16 year old male is referred by high school coach for a physical examination before joining the football team. His elder brother had died suddenly during football practise, no autopsy was done. The patient has a loud systolic murmur on chest auscultation. All of the following would be constant with hypertrophic cardiomyopathy, *except* : *(AIIMS Nov 99)*
A. A crescendo-decrescendo systolic murmur
B. Murmur radiating to neck
C. Brisk carotid upstroke
D. Increase in murmur during valsalva or standing

300. All are true about hypertrophic cardiomyopathy, *except* : *(AIIMS 1996)*
A. Systolic dysfunction
B. Concentric hypertrophy
C. Diastolic dysfunction
D. Double apical impulse

301. The murmur of hypertrophic obstructive cardiomyopathy is decreased in which of the following: *(AIIMS Nov. 2000)*
A. Supine position
B. Standing position
C. Valsalva maneuver
D. Amyl nitrate inhalation

302. A 68-year old man who has had a recent syncopal episode is hospitalized with congestive heart failure. His blood pressure is 160/80 mmHg. His pulse rate is 80 beats per minute, and there is a grade III/IV harsh systolic murmur. An echocardiogram shows a disproportionately thickened ventricular septum and systolic anterior motion of the mitral valve. Which of the following findings would most likely be present in this man : *(AIIMS Nov 99)*
A. Radiation of the murmur to the neck.
B. Decrease of the murmur with hand grip
C. Delayed carotid upstroke
D. Reduced left ventricular ejection fraction

303. Which of the following drugs are contraindicated in HOCM *(NBE)*
A. Verepamil
B. Propanalol
C. Digoxin
D. None of the above

304. The 9 month old child of a diabetic mother presents with tachypnea and hepatomegaly. Echocardiography of the heart showed normal cardiac morphology with asymmetric septal hypertrophy. Which of the following you will give to treat this child :
A. Digoxin *(AIIMS Nov. 2000)*
B. Frusemide
C. Propranolol
D. Isoptin

305. Aggravation of symptoms of angina in a patient when given nitrates is seen in : *(AIIMS June 2000)*
A. Aortic regurgitation
B. Mitral regurgitation
C. Single left coronary artery stenosis
D. Idiopathic hypertrophic subaortic stenosis

306. A 35-year-old farmer consulted a local medical practitioner for recurrent attacks of chest pain. His elder brother had similar complaints and had died suddenly at the age of 40 years. The farmer was advised to take nitroglycerine sublingually at the time of pain. However, the patient finds that the intensity of pain is increased by nitroglycerine. Most probably, he is suffering from : *(AIIMS Nov 02)*
A. Subacute bacterial endocarditis involving the aortic valve.
B. Hypertrophic obstructive cardiomyopathy.
C. Degenerative mitral regurgitation.
D. Chronic Type A dissection of aorta.

307. All are the true regarding hypertrophic obstructive cardiomyopathy, *except*: *(AIIMS Dec 97)*
A. Digitalis is useful
B. Left ventricular outflow obstruction
C. Asymmetrical septal thickness
D. Double apical impulse

## Pericardial Disease

### Cardiac Tamponade

308. All of the following are seen in cardiac tamponade *except*: *(AI 2004)*
A. Pulsus paradoxus
B. Diastolic collapse of right ventricle on echocardiogram
C. Electrical alternans
D. Kussmaul's sign

309. All of the following may be seen in patients of cardiac tamponade except: *(AI 06)*
A. Kussmaul's sign
B. Pulsus paradoxus
C. Electrical alternans
D. Right ventricular diastolic collapse on echocardiogram

310. All are features, seen in cardiac tamponade, *except*: *(AIIMS Dec 95)*
A. Raised JVP
B. Kussamaul sign
C. Rapid y descent
D. Pulsus paradoxus

311. Pulsus paradoxus is a characteristic feature of: *(AIIMS Dec 92)*
A. Constrictive pericarditis
B. Cardiac Tamponade

C. Hypertrophic obstructive cardiomyopathy
D. Restrictive cardiomyopathy

312. Beck's Triad is seen in: *(AI 2010)*
A. Constrictive Pericarditis
B. Cardiac tamponade
C. Right ventricular Myocardial Infarction (RVMI)
D. Restrictive Cardiomyopathy

313. Beck's triad of cardiac tamponade includes all, Except: *(AI 1991)*
A. Hypotension
B. Increased JVP
C. Muffled Heart sounds
D. Tachycardia

314. Beck's triad is? *(NBE)*
A. Increased heart sound, distended neck veins, hypotension
B. Increased heart sound, distended neck veins, hypertension
C. Muffled heart sound, distended neck veins, hypotension
D. Muffled heart wound, distended neck veins, hypertension

315. Beck's triad of cardic tamponade includes (select three correct options): *(PGI Dec 03)*
A. Hypotension
B. Neck vein distension
C. Paradoxical pulse
D. Silent heart
E. Tachycardia

316. A pt presents with engorged neck veins, BP 80/50 and pulse rate of 100 following blunt trauma to the chest : Diagnosis is: *(AI 2001)*
A. Pneumothorax
B. Right ventricular failure
C. Cardiac tamponade
D. Hemothorax

317. A young motorist suffered injuries in a major road traffic accident. He was diagnosed to have fracture of left femur and left humerus. He was also having fractures of multiple ribs anteriorly on both the sides. On examination the blood pressure was 80/60 mm Hg. and heart rate was 140/minute. The patient was agitated, restless, and tachypenic. Jugular veins were distended. Air entry was adequate in both the lung fields. Heart sounds were barely audible. Femoral pulses were weakly palpable but distally no pulsation could be felt. On priority basis, the immediate intervention would be :
A. Rapid blood transfusion. *(AIIMS Nov 02)*
B. Urgent pericardial tap.
C. Intercostal tube drainage on both the sides.
D. Fixation of left femur & repair of femoral artery

318. A post-operative cardiac surgical patient developed sudden hypotension, raised central venous pressure, pulsus paradoxus at the 4th post operative hour. The most probable diagnosis is:
A. Excessive mediastinal bleeding *(AI 2003)*
B. Ventricular dysfunction
C. Congestive cardiac failure
D. Cardiac tamponade

319. Kussmaul's sign is NOT seen in *(AI 2001)*
A. Restrictive cardiomyopathy
B. Constrictive pericarditis
C. Cardiac tamponade
D. RV infarct

320. Kussmaul's sign is classically described in: *(NBE)*
A. Restrictive Cardiomyopathy
B. Pericardial Tamponade
C. Constrictive pericarditis
D. Right Ventricular Infarct

321. Kussmaul's sign is seen in all of the following, Except: *(NBE)*
A. Restrictive Cardiomyopathy
B. Cardiac Tamponade
C. Constrictive pericarditis
D. Right Ventricular Infarct

322. A 30 year male patient presents to the emergency department with ahistory of acute breathlessness. On examination, JVP is increased and an inspiratory decline in systolic blood pressure of 14mm Hg is observed. Which of the following statements about the condition is true: *(PGI June 2008)*
A. Kussmaul's sign
B. Low ECG voltage
C. Prominent 'y' descent
D. Thickened Pericardium

323. Auenbrugger's sign is seen in: *(NBE)*
A. Pericardial Effusion
B. Constrictive Pericarditis
C. Aortic Regurgitation
D. Mitral Stenosis

324. All of the following are features of Moschowitz triad in Pericardial effusion, except: *(NBE)*
A. Widening of the cardiac silhouette
B. Bunting of cardiophrenic angle on the right side
C. An increase in cardiac dullness in the second intercostal space
D. An abrupt transition of pulmonary resonance to cardiac dullness.

325. Preferred Approach for Pericardiocentesis is: *(NBE)*
A. Sub-xiphoid
B. Left Parasternal
C. Right Parasternal
D. Apical

326. Most commonly utilized Intercostal Space for Pericardiocentesis is: *(NBE)*
A. Left 5th Intercostal Space
B. Left 6th Intercostal Space
C. Right 5th Intercostal Space
D. Right 6th Intercostal Space

327. Which of the following structures of the pericardium is insensitive to pain: *(NBE)*
   A. Fibrous Pericardium
   B. Parietal layer of Serous pericardium
   C. Visceral layer of Serous pericardium
   D. All of the above

328. Chest pain from pericardial inflammation in pericarditis is referred by: *(NBE)*
   A. Vagus nerve
   B. Phrenic nerve
   C. Trigeminal nerve
   D. Sympathetic nerves

329. Electric alternans is seen in: *(AI 1995)*
   A. Cardiac tamponade
   B. Restrictive cardiomyopathy
   C. Constructive pericarditis
   D. Right Ventricular MI (RVMI)

### Constrictive Pericarditis

330. Haemorrhagic pericarditis occurs in all of the following conditions *except.*: *(AIIMS May 03)*
   A. Transmural myocardial infarction.
   B. Dissecting aneurysm of aorta.
   C. Metastatic disease of pericardium.
   D. Constrictive pericarditis.

331. Which of the following is least likely to cause constrictive pericarditis? *(AIIMS Nov. 03)*
   A. Tuberculous pericardial effusion
   B. Staphylococcal effusion
   C. Post cardiac surgery
   D. Acute rheumatic fever

332. All of the following statements about chronic constrictive pericarditis are true except
   A. Commonest cause in India is 'Idiopathic'
   B. Kussmaul's sign is present *(PGI Dec 99)*
   C. Ascitis is not in proportion to edema
   D. Right ventricular End Diastolic pressure is raised

333. All of the following are features of constrictive pericarditis Except: *(PGI Dec 99)*
   A. Ascitis
   B. Retractile Apex
   C. Pericardial knock
   D. Acute pulmonary Edema

334. During ventricular pressure pulses square root wave is seen in – *(PGI Dec-98)*
   A. ASD
   B. MVPS
   C. Dilated cardiomyopathy
   D. Constrictive pericarditis

335. Restrictive cardiomyopathy may be differentiated from constrictive pericarditis by the following features (select two options): *(PGI June 02)*
   A. Diastolic pressures are equalized
   B. Pericardial effusion
   C. Thick pericardium is present
   D. RV size

336. Rapid X descent unlikely in *(PGI Dec 99)*
   A. Constrictive pericarditis
   B. Cardiac tamponade
   C. RVMI
   D. Restrictive cardiomyopathy

## Hypertension

### General

337. Most common cause of Hypertension in adults is:
   A. Essential Hypertension *(NBE)*
   B. Pheochromocytoma
   C. Renal Artery Stenosis
   D. Chronic Glomerulonephritis

338. Non-modifiable risk factor for hypertension: *(NBE)*
   A. Gender
   B. Obesity
   C. Salt intake
   D. Cultural characteristic acquired over time

339. Which of the following is a non-modifiable risk factor for hypertension? *(NBE)*
   A. Gender/sex
   B. High salt intake
   C. Alcohol addiction
   D. Dietary pattern due to strong socio-cultural influences

340. ypertension with Hypokalemia is seen in: *(NBE)*
   A. Bartter Syndrome
   B. Liddle's Syndrome
   C. Gitelman's Syndrome
   D. All of the above

341. A patient with Hypertension presents with Hypokalemia. Aldosterone levels and Renin levels are both elevated. The most likely diagnosis is: *(NBE)*
   A. Renal ArteryStenosis
   B. Primary Hyperaldosteronism (Conn's Syndrome)
   C. Addison's Disease
   D. Cushing's Syndrome

342. Management of uncomplicated essential hypertension is: *(NBE)*
   A. No need to treat
   B. Diet modification and exercise
   C. Diet modification, exercise & drugs
   D. Drugs alone

343. All of the followed drug combinations may be recommended for initial for management of hypertension, Except: *(AI 1991)*
   A. ACE inhibitors and Belablockers
   B. ACE inhibitors and calcium channel blockers
   C. Diuretics and ACE inhibitors
   D. Diuretic and Betablockers

344. First line drug choice for management of hypertension in patients with angina: *(NBE)*
   A. Beta Blockers
   B. ACE Inhibitors

C. Calcium Channel Blockers
D. Hydralazine

345. Initial Antihypertensive agent of choice in a patient with stable ischemic heart disease is *(NBE)*
A. Beta-Blockers
B. Alpha-Blockers
C. Calcium Channel Blockers
D. Ace Inhibitors

346. Which of the following drugs is MOST suitable for a 45-year-old diabetic with blood pressure 150/95 mmH g? *(NBE)*
A. Lisinopril
B. Amlodipine
C. Propranolol
D. Hydrochlorothiazide

347. A hypertensive diabetic is having proteinuria, antihypertensive of choice is: *(AIIMS May 95)*
A. Propanolol
B. Clonidine
C. Enalaprilat
D. Alpha methyldopa

348. An elderly patient presents with hypertension and diabetes, proteinuria without renal failure. Antihypertensive of choice is: *(AIIMS Nov 93)*
A. Furosemide
B. Methyldopa
C. Enalapril
D. Propranolol

349. A young patient presented with blood pressure of 190/120 mm of Hg without any clinical symptom and fundus examination is normal, treatment of choice:
A. Oral Nitroglycerine *(PGI June 03)*
B. I.V. Nitroglycerine
C. Oral Enalapril
D. IV Enalarpil
E. Sublingual short acting Nifedipine

350. Monogenic AD cause of HTN? *(PGI 2009)*
A. 17- $\alpha$ Hydroxylase deficiency
B. Gordon's Syndrome
C. Pregnancy Exacerbated HTN
D. Glucocortiocoid responsive HTN
E. Glucocorticoid Remediable Aldosteronism

## Hypertensive Crisis

351. Rapid Reduction of blood pressure is indicated in :
A. Acute Aortic Dissection *(AI 1991)*
B. Hypertensive Encephalopathy
C. Intracercbral haemorrhage
D. All of the above

352. Which of the following statements regarding hypertensive crisis is false: *(AIIMS Nov 1992)*
A. Hypertensive urgency is characterized by marked elevation of blood pressure and rapidly evolving end organ damage.
B. Hypertensive emergencies require immediate reduction of blood pressure within minutes
C. Hypertensive urgencies may be managed without extensive monitoring on an outpatient basis.
D. None of the above

353. All the following agents may be used for the management of hypertensive crisis Except:
A. Furosemide *(AIIMS May 1992)*
B. Nitroglyarine
C. Indapamide
D. Esmolal

354. A male patient presents with headache, profuse sweating and palpitations with a blood pressure of 180/120 mm Hg. The drug of choice would be
A. Nifedipine *(NBE)*
B. Labetalol
C. Prazocin
D. Phenoxy benzamine

355. All of the following drugs can be used in the management of hypertensive crises Except-
A. Hydralazene *(AIIMS May 1994)*
B. Trimethophan
C. Nifedipine
D. Indapamide

356. All of the following are used for hypertensive emergencies, Except: *(NBE)*
A. Fenoldapam
B. Nitroglycerine
C. Nitroprusside
D. Clonidine

357. All of the following are useful intravenous therapy for hypertensive emergencies except-
A. Fenodopam *(AIIMS May 03)*
B. Uradipil
C. Enalaprilat
D. Nifedipine

358. A patient presents with headache and profuse sweating. On examination his blood pressure is recorded as 200/120 mm Hg. Which of the following agents are not preferred (Select three best options)
A. Nifedipine *(PGI 2009)*
B. Sodium nitroprusside
C. Phenoxybenzomine
D. Methyldopa
E. Labetalol

359. In Accelerated HTN what is metabolic defect:
A. Normal non-ionic metabolic acidosis
B. Ionic gap met acidosis *(PGI June 2000)*
C. Hypomagnesemia
D. Metabolic alkalosis

## Renovascular Hypertension

360. Which of the following is the most specific and sensitive screening test for Renovascular Hypertension. *(AIIMS May 01)*
   A. HRCT
   B. CT Angiography
   C. Captopril enhanced radionucleatide scan
   D. MRI

361. Which of the following is the most specific screening test for renovascular hypertension: *(PGI 2008)*
   A. Magnetic Resonance Angiography (MRA)
   B. Spiral Computed Tomographic Angiography (CT Angiography)
   C. Captopril induced Radionucleotide Scan (Captopril Renogram)
   D. Duplex Doppler Ultrasonography

362. A 20 year old female presents with a blood pressure of 160/110 mm Hg. Clinical examination reveals a bruit in both flanks. Which of the following statements about this patient is not true (select one option) *(PGI 09)*
   A. Enalapril may deteriorate renal function
   B. Most definitive diagnostic procedure is contrast enhanced angiography
   C. Condition is nearly always bilateral
   D. Surgical intervention may be used
   E. Fibromuscular dysplasia is the likely cause in this patient

363. Most common cause of renal artery stenosis in young adults in India is: *(AIIMS Dec 97)*
   A. Atherosclerosis
   B. Non specific aorto-arteritis
   C. Fibro muscular dysplasia
   D. None of the above

364. Renal artery stenosis may occur in all of the following except: *(AI 2006)*
   A. Atherosclerosis
   B. Fibromuscular dysplasia
   C. Takayasu's arteritis
   D. Polyarteritis nodosa

## Pulmonary Hypertension

365. In primary pulmonary hypertension basic abnormality in gene lies in: *(AIIMS May 07)*
   A. Bone morphogenetic protein receptor II
   B. Endothelin
   C. Homebox gene
   D. PAX – 11

366. Not seen in pre capillary pulmonary hypertension:
   A. ↑ pressure in pulm. circulation *(PGI June 98)*
   B. ↑ capillary pressure
   C. Rt-vent.hypertrophy
   D. ↑ Pulmonary wedge pressure

367. Precapillary Pulmonary hypertension is caused by all Except: *(PGI June 03)*
   A. Mitral stenosis
   B. Pulmonary vasculitis
   C. Primary pulmonary hypertension
   D. Thromboembolism

368. All are causes of pulmonary hypertension except-
   A. Hyperventilation *(AIIMS Nov 07)*
   B. Morbid obesity
   C. High altitude
   D. Fenfluramine

369. Pulmonary hypertension may occur in all of the following conditions except- *(AIIMS Nov 06)*
   A. Toxic oil syndrome
   B. Progressive systemic sclerosis
   C. Sickle cell anemia
   D. Argemone mexicana poisoning

370. Pulmonary hypertension in COPD is due to all, Except: *(PGI Dec 97)*
   A. Hypoxia
   B. Pulmonary vasoconstriction
   C. High lung volume
   D. Bronchoconstriction

## Aortic Dissection

371. A 50 year old man, an alcoholic and a smoker presents with a 3 hour history of increasing shortness of breath. He started having this pain while eating, which was constant and radiated to the back and interscapular region. He was a known hypertensive. On examination, he was cold and clammy with a heart rate of 130/min, and a BP of 80/40 mmHg. JVP was normal. All peripheral pulses were present and equal. Breath sounds were decreased at the left lung base and chest x-ray showed left pleural effusion. Which one of the following is the most likely diagnosis? *(AI 2005)*
   A. Acute aortic dissection.
   B. Acute myocardial infarction.
   C. Rupture of the esophagus.
   D. Acute pulmonary embolism.

372. Manifestation of Acute Dissection include all of the following, Except: *(PGI June 01)*
   A. Pericardial effusion
   B. AR
   C. MR
   D. AMI
   E. Limb ischemia

373. All of the following factors predispoase to Aortic dissection, Except: *(PGI June 02)*
   A. Systemic hypertension
   B. Coarctation of aorta
   C. In Ist trimester pregnancy
   D. Takayasu's arteritis
   E. Marfan syndrome

374. All of the following agents may be used in the treatment of Aortic dissection, Except (select two options): *(PGI Dec 05)*
A. Propanolol
B. Diazoxide
C. Na nitroprusside
D. Hydralazine
E. Labetolol

## Cardiopulmonary Resuscitation

375. The 2010 AHA Guidelines for CPR during Basic Life Support Recommend: *(AIIMS 2013)*
A. Airway – Breathing – Compression (A-B-C)
B. Compression – Breathing- Airway ( C-B-A)
C. Compression- Airway – Breathing (C-A-B)
D. Breathing – Airway – Compression (B –A-C )

376. Key issues and major changes in the 2010 AHA Guidelines for CPR for lay rescuer in adult CPR include all of the following Except: *(AIIMS 2013)*
A. Change in CPR Sequence: C-A-B Rather than A-B-C
B. Emphasis on "Look, Listen, and Feel' for Breathing
C. Chest Compression Rate: At Least 100 per Minute
D. Chest Compression Depth to at least 2 inches (5 cm).

377. The 2010 AHA Guidelines for CPR during Basic Life Support for neonates Recommends: *(AIIMS 2013)*
A. Airway – Breathing – Compression (A-B-C)
B. Compression – Breathing- Airway (C-B-A)
C. Compression- Airway – Breathing (C-A-B)
D. Breathing – Airway – Compression (B –A-C)

378. Which of the following is the preferred antiarrhythmic agent in a patient with cardiac arrest: *(AIIMS 2013)*
A. Amiodarone
B. Lidocaine
C. Procainamide
D. Atropine

379. According to the 2010 ACLS Guidelines by AHA, which of the following pharmacological agents is not used in the management of cardiac arrest : *(AIIMS 2013)*
A. Epinephrine
B. Vasopressin
C. Atropine
D. Amiadorone

380. A young patient sustains cardiac arrest, in the medical ward. Immediate defibrillation is advised when the ECG shows: *(AI 1992)*
A. Ventricular Tachycardia
B. Asystole
C. Electromechanical dissociation
D. Persistant Bradyarrhythmia

381. True regarding cardio pulmonary resuscitation is: *(AIIMS Dec 98)*
A. Most common presentation in ECG is asystole
B. Compression to ventilation ratio is 5:1
C. Adrenaline is given if cardioversion fails
D. Calcium gluconate is given immediately

382. All of the following may be used in the treatment of cardiac arrest following ventricular fibrillation, Except (Select two best options) *(PGI 09)*
A. Atropine
B. External cardiac pacing
C. Epinephrine
D. Antiarrhythmic agents
E. Vasopressin

383. True regarding cardio pulmonary resuscitation is– *(AIIMS Dec 97)*
A. Most common presentation in ECG is asystole
B. Compression to ventilation ratio is 5:1
C. Adrenaline is given if cardioversion fails
D. Calcium gluconate is given immediately

384. Asynchronous cadioversion is given in:
A. AF *(AIIMS Nov 98)*
B. Ventricular fibrillation
C. Atrial flutter
D. Ventricular tachycardia

385. What would be the first line of treatment is a patient who develops ventricular fibrillation after intravenous injection of potassium chloride- *(AIIMS May 2004)*
A. Cardiac massage
B. I.V Adrenaline
C. Defibrillation
D. IPPV

386. The best chances of recovery after successful cardiopulmonary resuscitation are seen in: *(AI 1993)*
A. Ventricular Tachycardia
B. Ventricular Fibrillation
C. Asystole
D. Electromechanical dissociation

387. In cardio pulmonary resuscitation, calcium can be given in all, EXCEPT- *(AIIMS Dec 97)*
A. Hypocalcemia
B. Hypokalemia
C. Hyperkalemia
D. Calcium channel blocker

## Cardiac Tumors

388. Most common tumour of heart is: *(AI 99)*
A. Myxoma
B. Rhabdomyosarcoma
C. Fibroma
D. Leiomyosarcoma

389. The commonest tumor of the myocardium is :
A. Myxoma *(AI 94)*
B. Rhabdomyoma
C. Sarcoma
D. Fibroma

390. Which of the following statements about atrial myxomas is true *(NBE)*
A. Most common in Left Atrium
B. More common in Males
C. Distant metastasis are seen
D. Most myxomas are familial

391. All of the following statement about atrial myxomas are true, except: *(NBE)*
A. Most common site is Left Atrium
B. Most common in young individuals
C. Distant metastasis are rare
D. Most myxomas are familial

392. All of the following are clinical features of myxoma, *except* : *(AI 2002)*
A. Fever
B. Clubbing
C. Hypertension
D. Embolic phenomenon

393. True statement about cardiac myxoma is : *(AI 1999)*
A. Commonest site is left atrium
B. Rarely reoccurs after excision
C. Distant metastasis are seen
D. More common in females

394. Gradient in pulmonary artery wedge pressure and left ventricular end diastolic pressure is seen in
A. Aortic regurgitation *(AIIMS June 2000)*
B. Constrictive pericarditis
C. Left atrial myxoma
D. Pulmonary thromboembolism

## Rheumatic Fever

395. Which is a minor criteria for diagnosis of RF according to modified Jones criteria?
A. ASO titre *(AI 2007)*
B. Past History of Rheumatic Fever
C. Fever
D. Subcutaneous nodules

396. Which of the following is a minor criteria for diagnosis of Rheumatic Fever (RF) according to modified Jones criteria? *(AI 2007)*
A. ASO titre
B. Past History of Rheumatic Fever
C. Fever
D. Subcutaneous nodules

397. Which of the following is not included in Jone's Major Criteria *(AIIMS Nov 2010)*
A. Pancarditis
B. Chorea
C. Subcutancous nodule
D. High ESR

398. All of the following are major criteria in the diagnosis of Acute Rheumatic Fever, Except: *(AIIMS 2013)*
A. Migratory Polyarthralgia
B. Subcutaneous Nodules
C. Chorea
D. Carditis

399. Major criteria of Rheumatic fever include (select three options) – *(NBE)*
A. Chorea
B. Erythema nodosum
C. Arthritis
D. Fever
E. Carditis

400. True about acute rheumatic fever (select three options)
A. Chorea *(PGI Dec-02)*
B. Erythema nodosum
C. Arthritis
D. Caused by antecedent $\alpha$ - hemolytic streptococcus infection
E. Carditis

401. Characteristic feature of Rheumatic carditis is :
A. Pericarditis *(AI 99)*
B. Endocarditis
C. Myocarditis
D. Pancarditis

402. A 10 year old boy, Pappu, died of acute rheumatic fever. All the following can be expected at autopsy except : *(AI 02)*
A. Ashoff nodules
B. Rupture of chordae tendinae
C. Mc Callum patch
D. Fibrinous pericarditis

403. Diagnostic feature in rheumatic heart disease is :
A. Aschoff's nodule *(AI 97)*
B. Mc Callman patch
C. Adeno Carcinoma
D. Alveolar cell Carcinoma

404. Aschoff's nodules are seen in : *(AI 05)*
A. Subacute bacterial endocarditis
B. Libman-sacks endocarditis
C. Rheumatic carditis
D. Nonbacterial thrombotic endocarditis

405. McCallum's patch is diagnostic of : *(AI 95)*
A. Infective endocarditis
B. Rheumatic endocarditis
C. Myocardial infarction
D. Tetralogy of fallout (TOF)

406. All are true about rheumatic fever, *except* :
A. Common in poor socioeconomic group
B. Develops after streptococcal pharyngitis
C. Communicable disease *(AIIMS June 99)*
D. Seen in 5-15 year of children

407. True about Rheumatic fever – *(PGI Dec 03)*
A. Chorea is aggravated during pregnancy
B. Chorea & arthritis co-existing
C. Subcutaneous nodules are tender
D. Erythema multiforme seen

408. True statement about Rheumatic fever in children (select two options)– *(PGI Dec- 03)*
A. Polyarthritis
B. Caused by $\alpha$ hemolytic streptococci
C. Erythem marginatum is most common manifestation

D. MC valve involvement is Mitral
E. Erythema marginatum is common in face

409. True about Erythema Marginatum in Acute Rheumatic fever is: *(PGI Dec 01)*
A. Pruiritic
B. Commonly involves face
C. Common manifestation of Acute Rheumatic fever
D. Usually associated with carditis

410. True about subcutaneous nodule in Rheumatic fever (select two options)- *(PGI Dec 03)*
A. Non tender
B. Most common manifestation
C. Present in extensor surfaces
D. Associated with arthritis

411. Earliest valvular lesion in a case of acute rheumatic fever is- *(AIIMS May 94)*
A. Mitral regurgitation (MR)
B. Aortic Regurgitation (AR)
C. Mitral stenosis (MS)
D. Aortic Stenosis (AS)

## Congenital Heart Disease

### General

412. The commonest mode of inheritance of congenital heart disease is *(AI 2002)*
A. Autosomal dominant
B. Autosomal recessive
C. Sex linked dominant
D. Multifactorial

413. Cardiac abnormality seen with Noonan's syndrome is: *(AIIMS May 95)*
A. VSD
B. ASD
C. Pulmonary stenosis
D. Coarctation of aorta

414. Differential cyanosis is seen in: *(AI 1996)*
A. ASD
B. VSD
C. PDA
D. All of the above

415. Pressure difference of 5mm Hg between the two upper limbs occurs in which congenital heart disease: *(NBE)*
A. TOF
B. TGA
C. HOCM
D. Supra –valvular aortic stenosis

416. Congenital heart disease associated with decreased pulmonary blood flow - *(PGI Dec 04)*
A. Truncus arteriosus
B. TAPVC
C. Ebstein's anomaly
D. Complete TGA
E. Single ventricle with pulmonary stenosis

417. All of the following are cyanotic heart diseases, Except : *(PGI June 05)*
A. TOF
B. PDA
C. Tricuspid Atresia
D. Eisenmenger's complex

418. All can cause recurrent pulmonary infection except: *(AIIMS Sep 96)*
A. VSD
B. Recurrent LVF
C. TOF
D. ASD

### Tetralogy of Fallot

419. The following features are true for tetralogy of Fallot, *except*: *(AI 2006)*
A. Ventricular septal defect
B. Right ventricular hypertrophy
C. Atrial septal defect
D. Pulmonary stenosis

420. Essential criteria for TOF includes all except – *(AIIMS Nov 07)*
A. Valvular stenosis
B. Infundibular stenosis
C. Over riding of aorta
D. RVH

421. Which of the following is a component of Pentalogy of Fallot: *(AI 2007)*
A. Atrial Septal Defect (ASD)
B. Patent Ductus Arteriosus (PDA)
C. Coarctation of Aorta (COA)
D. Left Venticular Hypertrophy (LVH)

422. All of the following statements about Tetralogy of fallot are true, Except *(NBE)*
A. JVP is normal
B. Second Heart sound is single
C. Ejection systolic murmur is third left intercostal space
D. First Heart sound is soft

423. All of the following are true regarding Tetralogy of fallot except – *(AIIMS May 05)*
A. Ejection systolic murmur in second intercostal space
B. Single second heart sound
C. Predominantly left to right shunt
D. Normal jugular venous pressure

424. In which of the following a 'Coeur en Sabot' shape of the heart is seen: *(AI 2004)*
A. Tricuspid atresia
B. Ventricular septal defect
C. Transposition of great arteries
D. Tetralogy of Fallot

425. Blalock and Taussig shunt is done between: *(AI 2006)*
A. Aorta to pulmonary artery
B. Aorta to pulmonary vein
C. Subclavian artery to pulmonary vein
D. Subclavian vien to artery

426. Potts shunt is : *(AI 2001)*
   A. Rt subclavian artery to rt pulmonary artery
   B. Descending aorta to left pulmonary artery
   C. Left subclavian to left pulmonary artery
   D. Ascending aorta to right pulmonary artery

427. Fallots tetralogy manifestation (select two options) –
   A. Left axis deviation *(PGI June 06)*
   B. Left ventrucular hypertrophy
   C. VSD
   D. Blalock taussig shunt is between pulmonary artery & subclavian artery
   E. Morphine is contraindicated in cyanotic spells

## Atrial Septal Defect

428. A young female presents with history of dyspnoea on exertion. On examination, she has wide, fixed split S2 with ejection systolic murmur (III/VI) in left second intercostal space. Her EKG shows left axis deviation. The most probable diagnosis is : *(AIIMS May 03)*
   A. Total anomalous pulmonary venous drainage.
   B. Tricuspid atresia. *(AIIMS May 04)*
   C. Ostium primum atrial septal defect.
   D. Ventricular septal defect with pulmonary arterial hypertension.

429. All of the following are true about ASD *except*:
   A. Right atrial hypertrophy *(AI 2001)*
   B. Left atrial hypertrophy
   C. Right ventricular hypertrophy
   D. Pulmonary hypertension

430. True about ASD : *(AI 1998)*
   A. Foramen ovale is patent
   B. Left parasternal heeve is due to increased pulmonary artery flow
   C. $S_2$ is wide and variable
   D. Systolic murmur is due to rapid flow of blood across the shunt.

431. Presence of a pansystolic murmur of Mitral Regurgitation with left axis deviation in a patient with ASD suggest: *(NBE)*
   A. TGA
   B. Ostium secondum with floppy mitral valve
   C. Ostium primum with floppy mitral valve
   D. Pulmonary Hypertension

432. In which of the following conditions left atrium is not enlarged: *(AI 2006)*
   A. Ventricular septal defect
   B. Atrial septal defect
   C. Aortopulmonary window
   D. Patent ductus arteriosus

## Ventricular Septal Defect (VSD)

433. True about V.S.D. is, all *except* : *(AIIMS June 97)*
   A. Small hole closes spontaneously
   B. Defect is usually in membranous part
   C. Endocarditis is commonest complication
   D. Pulmonary oligemia in chest X-ray

## Patent Ductus Arteriosus (PDA)

434. Differential cyanosis is seen in: *(AI 1996)*
   A. ASD
   B. VSD
   C. PDA
   D. All of the above

435. True statement about Ductus Arteriosus is : *(AI 2000)*
   A. It undergoes anatomic closure within 24 hrs of birth
   B. Forms the ligamentum venosum in later life
   C. It is induced to close by high levels of prostaglandins
   D. May cause a machinary murmur by its patency.

436. MC cause of death in adult with PDA is –
   A. CCF *(PGI Dec 99)*
   B. Infective endocarditis
   C. Rupture
   D. Embolism

## Tricuspid Atresia

437. All of the following are characteristics features of Tricuspid Atresia Except: *(AIIMS Dec 98)*
   A. Left Axis deviation
   B. Right ventricular hypoplasia
   C. Pulmonary vascularity is diminished
   D. Splitting of $S_2$

438. A five year old child presents with Left ventricular hypertrophy and central cyanosis. What is the most probable diagnosis? *(AIIMS Nov 2000)*
   A. Tricuspid atresia
   B. Eisenmenger syndrome
   C. Tetrology of Fallot
   D. Total anomalous pulmonary venous drainage

439. A child presents with LVH and pulmonary complications. ECG shows left axis deviation. Most likely diagnosis is: *(AI 2001)*
   A. TOF
   B. Tricuspid atresia
   C. TAPVC
   D. VSD

440. Right axis deviation is seen in all except –
   A. VSD *(AIIMS June- 98)*
   B. Tricuspid atresia
   C. Pulmonary atresia
   D. ASD

441. Ebstein's anomaly is characterized by: *(NBE)*
   A. Upward displacement of an abnormal tricuspid valve into right atrium
   B. Downward displacement of an abnormal tricuspid valve into right ventricle
   C. Ventricularized right atrium
   D. Atrialized left ventricle

## Coarctation of Aorta

442. A patient complains of intermittent claudication, dizziness and headache; likely cardiac lesion is:
A. TOF *(AI 2001) (AIIMS Nov 2000)*
B. ASD
C. PDA
D. Coarctation of aorta

443. A 1-month-old boy is referred for failure to thrive. On examination, he shows feature of congestive failure. The femoral pulses are feeble as compared to branchial pulses. The most likely clinical diagnosis is: *(AI 2006)*
A. Congenital aortic stenosis
B. Coarctation of aorta
C. Patent ductus arteriosus
D. Congenital aortoiliac disease

444. All of the following are seen in Coarctation of Aorta, Except: *(NBE)*
A. Diminution of femoral pulsations
B. High incidence of associated Bicuspid aortic valve
C. Left ventricular Hypertrophy
D. Boot Shaped Heart

445. A 27 year old man in noted to have blood pressure of 170/100 mmHg. He has prominent aortic ejection click and murmurs heard over the ribs on the both sides anteriorly and over the back posterioly. In addition.the pulses in the lower extremities are feeble and he complains of mild claudication with exertion. The most likely diagnosis is *(AIIMS Nov 04)*
A. Artial septal defect
B. Aortic stenosis
C. Coarctation of the aorta
D. Cardiomyopathy

446. A 4 1/2- year-old girl always had to wear warm socks even is summer season. On physical examination, it was noticed that she had high blood pressure and her femoral pulse was weak as compared to radial and carotid pulse. A chest radiograph showed remarkable notching of ribs along with their lower borders. This was due to: *(AIIMS Nov 02)*
A. Femoral artery thrombosis.
B. Coarctation of aorta.
C. Raynaud's disease.
D. Takayasu's arteritis.

447. A Ten year old boy presents to the pediatric emergency unit with seizures. Blood pressure in the upper extremity measured as 200/140 mm Hg. Femoral pulses were not palpable. The most likely diagnosis amongst the following is: *(AI 2010)*
A. Takayasu Aortoarteritis
B. Renal parenchymal disease
C. Grandmal seiures
D. Coarctation of Aorta

448. A child presented with headache, dizziness, intermittent claudication with occassional dyspnoea. The most probable diagnosis in : *(AI 1999)*
A. ASD
B. PDA
C. TOF
D. Coarctatation of aorta

449. A 20 year young man presents with exert ional dyspnoea, headache, and giddiness. On examination, there is hypertension and LVH. X-ray picture shows notching of the anterior ends of the ribs. The most like diagnosis is : *(AI 2002)*
A. Phaeochromocytoma
B. Carcinoid syndrome
C. Coarctation of the aorta
D. Superior Mediastinal syndrome

450. All the following findings would be expected in a person with coarctation of the aorta *except* : *(NBE)*
A. A systolic murmur across the anterior chest and back and a high-pitched diastolic murmur along the left sternal border
B. B. A higher blood pressure in the right arm than in the left arm *(AIIMS Nov 99)*
C. Inability to augment cardiac output with exercise
D. Persistent hypertension despite complete surgical repair

451. True about co-arctation of aorta : *(AI 1999)*
A. Most common site is distal to the origin of the left subclavian artery
B. Most common age of presentation is at 15-20years
C. Superior rib notching is due to erosion by dilated collateral vessels
D. Right ventricular hypertrophy is prominent

452. Which condition is most commonly associated with coarctation of aorta? *(AI 2008)*
A. PDA
B. Bicuspid aortic valve
C. Aortic stenosis
D. VSD

453. Coarctation of Aorta is most commonly associated with: *(AI 2011)*
A. Bicuspid Aortic valve
B. Patent Dustus Arteriosus (PDA)
C. Ventricular Septal Defect (VSD)
D. Atrial Septal Defect (ASD)

454. Coarctation of aorta is associated with all, *except*:
A. Turner's syndrome *(AIIMS June 98)*
B. Bicuspid aortic valve
C. Pulmonary stenosis
D. Atresia of aortic arch

455. Coarctation of aorta may be associated with all of the following *except* : *(AI 1997) (AIIMS 1995)*
A. Bicuspid aortic valve
B. Turner's syndrome

C. Renal artery stenosis
D. PDA

456. Coarctation of the aorta is common in which syndrome: *(AI 1995)*
A. Down's
B. Turner's
C. Klinefelter's
D. Noonan's

457. Inferior Rib notching is seen in all except-
A. Coarctation of aorta *(AIIMS June 2000)*
B. Classical blalock tausing operation
C. SVC obstruction
D. Neurofibromatosis

458. Ribnotching of 4-9$^{th}$ ribs with double bulging is seen in : *(AI 1998)*
A. Aortic aneurysm
B. Aortic dessection
C. Co-arctation of aorta
D. Diaphragmatic hernia

459. All of the following causes death in coarctation of Aorta except: *(PGI June 2000)*
A. Infective endocarditis
B. CCF
C. Intra cranial hemorrhage
D. Anterior MI

## Total Anomalous Pulmonary Venous Connection (TAPVC)

460. The most common type of total anomalous pulmonary venous connection is: *(AI 2005)*
A. Supracardiac.
B. Infracardiac.
C. Mixed.
D. Cardiac.

461. All of the following statements regarding total anomalous pulmonary connection are true except:
A. The total pulmonary venous blood reaches the right atrium *(AI 97)*
B. Always associated with a VSD
C. The oxygen saturation of the blood in the pulmonary artery is higher than that in the aorta
D. Infracardiac type is always obstructive

462. Snowman Shaped Heart is typically seen in: *(NBE)*
A. Tetralogy of Fallot
B. Total Anomalous Pulmonary Venous Connection
C. Transposition of Great Vessels
D. Coarctation of Aorta

## Transposition of Great Vessels ( TGV)

463. A five day old, full term male infant was severely cyanotic at birth. Prostaglandin E was administered initially and later ballooned atrial septosomy was done which showed improvement in oxygenation. The most likely diagnosis of this infant is : *(AI 2004)*
A. Tetralogy of Fallot
B. Transposition of great vessels
C. Truncus Arteriosus
D. Tricuspid Atresia

## Anamolous Coronary Artery

464. A neonate has recurrent attacks of abdominal pain, restless irritability and diaphoresis on feeding. Cardiac auscultation reveals a nonspecific murmur. He is believed to be at risk for M.I. Likely diagnosis here is: *(AI 2001)*
A. ASd
B. VSd
C. TOF
D. Anomalous coronary artery

## Eissenmerger's Syndrome

465. Eisenmenger syndrome is characterized by all except:
A. Return of left ventricle & right ventricle to normal size. *(AI 2005)*
B. Pulmonary veins not distended.
C. Pruning of peridpheral pulmonary arteries.
D. Dilatation of central pulmonary arteries.

## Miscellaneous

466. The heart lesion *not* found in Congenital Rubella infection is: *(AI 1995)*
A. ASD
B. VSD
C. PDA
D. PS

467. Sustained severe hypertension in children is most commonly suggestive of: *(AI 1995)*
A. Coarctation of aorta
B. Pheochromocytoma
C. Renal paranchymatous disease
D. Drug induced

468. NADA's criteria are used for: *(AI 1996)*
A. Assessment of child for degree of dehydration
B. Assessment of child for degree of malnutrition
C. Assessment of child for presence of heart disease
D. Assessment of child for degree of mental retardation

## Endocarditis

469. Diagnostic criterion for Infective Endocarditis include all, Except: *(NBE)*
A. Positive Echocardiogram
B. Positive Blood culture
C. Raised ESR
D. Positive Rheumatoid Factor

470. Infective endocarditis is least likely to occur in:
A. Atrial septal defect *(AIIMS June 97)*
B. Small ventricular septal defect
C. Mitral valve prolapse *(AIIMS June 98)*
D. Tetrology of Fallot's *(AIIMS May 01)*

471. Which of the following is least likely to be associated with Infective Endocarditis: *(AI 2012)*
A. Small ASD
B. Small VSD
C. Mild MR
D. Mild MS

472. Bacterial endocarditis is rarely seen in- *(AI 96)*
A. VSD
B. PDA
C. MVP
D. secundum ASD

473. Infective endocarditis is commonly seen in all except-
A. Small VSD *(AIIMS June 98)*
B. Tetralogy of fallot
C. PDA
D. ASD

474. Infective endocarditis is least common in-
A. Mitral stenosis *(AIIMS Nov 93)*
B. Aortic stenosis
C. VSD
D. ASD

475. Least common site for vegetation is-
A. Aortic Stenosis (AS) *(AIIMS May 94)*
B. Mitral Stenosis (MS)
C. Mitral Regurgitation (MR)
D. Atrial Septal Defect (ASD)

476. Least common cause of endocarditis is:
A. A.S.D *(AIIMS June 97)*
B. P.D.A
C. T.O.F.
D. V.S.D.

477. Infective endocarditis is most commonly seen in:
A. ASD *(AIIMS Feb 97)*
B. VSD
C. PDA
D. Pulmonary stenosis.

478. Endocarditis is most commonly seen in :
A. Mitral stenosis *(AIIMS May 95)*
B. Mitral regurgitation
C. Mitral valve prolapse
D. Tricuspid stenosis

479. Mitral valve vegetations do not usually embolise to :
A. Lung *(AI 2001) (AIIMS Nov 2001)*
B. Liver
C. Spleen
D. Brain

480. Most common heart valve involved in IV drug user is: *(AIIMS Feb 97)*
A. Mitral valve
B. Aortic valve
C. Pulmonary valve
D. Tricuspid valve

481. A woman has septic abortion done; vegetation on tricuspid valve is likely to go to: *(AI 2001)*
A. Septic infarcts to lung
B. Liver
C. Spleen infarcts
D. Emboli to brain

482. Osler's nodes are seen at : *(AIIMS June 98)*
A. Heart
B. Knee joint
C. Tip of Palm & Sole
D. Anterior abdominal wall

483. Roth's spots are seen in: *(NBE)*
A. Infective Endocarditis
B. Rheumatic Endocarditis
C. Central Retinal Arterial Occlusion (CRAO)
D. Typhoid

484. Not a feature of infective endocarditis is :
A. Myocardial abscess *(AIIMS Feb 97)*
B. Vegetations along cusps
C. Thrombus in left atria
D. Perforation of cusp

485. Which of the following is least likely to cause infective endocarditis : *(AI 06)*
A. Staphylococcus albus
B. Streptococcus faecalis
C. Salmonella typhi
D. Pseudomonas aeruginosa

486. Bacterial endocarditis is most commonly caused by –
A. $\alpha$ -Hemolytic Streptococci *(AI 06)*
B. $\beta$ -Hemolytic Streptococci
C. Staphylococcus aureus
D. Cardiobaterium
E. Staph epidermidis

487. A patient with a prosthetic heart valve develops endocarditis eight months after valve replacement. Most likely organism responsible is:
A. Staphylococcus Aureus *(AIIMS Nov 2010)*
B. Staphylococcus Epidermidis
C. Streptococcus Viridans
D. HACEK group

488. Acute Infective Endocarditis with abscess formation is most commonly associated with *(NBE)*
A. Listeria
B. Staphylococcus
C. Streptococcus
D. Enterococcus

489. Which of the following is recommended for culture sampling in Infective Endocarditis: *(NBE)*
A. 2 culture sets separated by at-least 1 hour over 24 hours
B. 2 culture sets separated by at-least 2 hours over 24 hours
C. 3 culture sets separated by at-least 1 hr over 24hrs
D. 3 culture sets separated by at-least 2 hours over 24 hours

490. Antiboiotic Prophylaxis for infective endocarditis is indicated in: *(NBE)*
   A. Isolated secundum ASD
   B. Mitral valve prolapse without regurgitation
   C. Prior coronary artery bypass graft
   D. Coarctation of aorta

491. In a patient of heart disease antibiotic prophylaxis for dental extraction is: *(NBE)*
   A. Amoxycillin
   B. Imipenam
   C. Gentamycin
   D. Erythromycin

492. All of the following statements about Fungal Endocarditis are true except *(NBE)*
   A. Candida is the most common agent
   B. Life-long antifungal agents may be required
   C. Surgical treatment is often recommended
   D. Good prognosis with treatment

493. Which of the following have most friable vegetation:
   A. Infective endocarditis *(AI 2010)*
   B. Libman Sack's endocarditis
   C. Rheumatic heart disease
   D. SLE

*494.* Vegetations on undersurface of A.V. valves are found in: *(AI 2001)*
   A. Acute Rheumatic corditis
   B. Limban Sack's endocarditis
   C. Non thrombotic bacterial endocarditis
   D. Chronic rheumatic carditis

495. A young female presents with verrucous vegetations on the surface of mitral valve cusps. The most likely diagnosis is: *(NBE)*
   A. Rheumatic Fever
   B. Marantic Endocarditis
   C. Libman Sacks Endocarditis
   D. Infective Endocarditis

496. Libman Sack's Endocarditis is seen in:
   A. SLE *(NBE)*
   B. Rheumatic Fever
   C. Carcinoid
   D. Infective Endocarditis

497. Flat vegetations in pockets of valves are due to :
   A. Rheumatic heart disease *(AI 2000)*
   B. Libman sacks Endocarditis
   C. NBTE
   D. Infective endocarditis

498. Site of lesion in endocarditis of RHD is –
   A. Along line of closure of valves
   B. Both sides of valves *(PGI Dec-97)*
   C. Valve cusps
   D. Free margin of valves

499. Firm warty vegetations along the line of closure of valves is due to : *(AI 2000)*
   A. Rheumatic heart disease
   B. Libman Sacks Endocarditis
   C. NBTE
   D. Infective Endocarditis

## Cardiac Involvement in Carcinoid Syndrome and Lupis

500. Carcinoid syndrome produces valvular disease primarily involving- *(AIIMs May 05)*
   A. Pulmonary valves
   B. Tricuspid valves
   C. Mitral valves
   D. Aortic valves

501. Charachteristic pathological finding in carcinoid heart disease is: *(AI 2010)*
   A. Fibrous endocardial thickening of Right ventricle, Tricuspid valve & Pulmonary valve
   B. Endocardial thickening of Tricuspid valve with severe Tricuspid Stenosis
   C. Collagen rich, elastic deposits in endocardium of right ventricle and Pulmonary valve
   D. Calcification of Tricuspid and Pulmonary valve

502. Carcinoid syndrome produces valvular disease primarily involving: *(AIIMS May 04)*
   A. Venous valves
   B. Tricuspid valve
   C. Mitral valve
   D. Aortic valve

503. Most common valvular lesion in Carcinoid Syndrome of the Heart is: *(NBE)*
   A. Aortic Stenosis
   B. Mitral Stenosis
   C. Tricuspid regurgitation
   D. Aortic regurgitation

504. Most common valvular lesion in carcinoid syndrome of heart is: *(NBE)*
   A. Aortic stenosis
   B. Tricuspid regurgitation
   C. Mitral Stenosis
   D. Aortic Regurgitation

505. In carcinoid syndrome, the aprt of heart mostly affected is: *(PGI Dec 97)*
   A. Outflow tract of RV
   B. Inflow tract of RV
   C. Inflow tract of LV
   D. Outflow tract LV

506. Most common presentation of cardiac lupus is
   A. Myocarditis *(NBE)*
   B. Pericarditis
   C. Endocarditis (Libman-Sacks)
   D. Aortic Regurgitation

## Sudden Cardiac Death

507. Sudden cardiac death may occur in all of the following except : *(AI 06)*
   A. Dilated cardiomyopathy
   B. Hypertrophic cardiomyopathy
   C. Eisenmenger's syndrome
   D. Ventricular septal defect

## Miscellaneous

508. S.A. node acts as a pacemaker of the heart because of the fact that it: *(AI 05)*
   A. Is capable of generating impulses spontaneously
   B. Has rich sympathetic innervations
   C. Has poor cholinergic innervations
   D. Generates impulses at the highest rate

509. Highest rate of impulse generation is given in: *(NBE)*
   A. SA node
   B. AV node
   C. Bundle of HIS
   D. Purkinje system

510. Highest conduction rate in m/s is observed in:
   A. SA node *(AI 1995)*
   B. AV node
   C. Bundle of His
   D. Purkinje system

511. Speed of conduction is fastest in: *(PGI Dec 05)*
   A. AV node
   B. SA node
   C. Bundle of His
   D. Purkinje system
   E. Ventricular muscle

512. Least conduction velocity is seen in: *(PGI Dec 98)*
   A. AV node
   B. Purkinje fibres
   C. Bundle of his
   D. Ventricular myocardial fibres

513. Which of the following is the order of activation after stimulation of Purkinji fibrs is : *(AIIMS Dec 95)*
   A. Septum –> Endocardium –> Epicardium
   B. Endocrdium –> Septum –> Epicardium
   C. Epicardium –> Septum –> Endocardium
   D. Septum –> Epicardium –> Endocardium

514. The right coronary artery supplies all of the following parts of the conducting system in the heart except:
   A. SA Node *(AI 2003)*
   B. AV Node
   C. AV Bundle
   D. Right Bundle branch

515. If circumflex artery gives the posterior intervene-tricular branch, this circulation is described as:
   A. Right dominance *(AIIMS Nov 07)*
   B. Left dominance
   C. Codominance
   D. Undetermined

516. During the cardiac cycle the opening of the aortic valve takes place at the : *(AI 04)*
   A. Beginning of systole
   B. End of isovolumetric contraction
   C. End of diastole
   D. End of diastasis

517. At the end of isometric relaxation phase :
   A. Atrioventricular valves open *(AI 2000)*
   B. Atrioventricular valves close
   C. Corresponds to peak of "C" wave in JVP
   D. Corresponds to T wave in ECG

518. Of the following which one correlates with isovolumic contraction phase: *(AIIMS June 98)*
   A. AV opening and aortic and pulmonary valve closure
   B. AV closure and aortic & pulmonary valve opening
   C. Both valves are closed
   D. Both valves are open

519. Isovolumic relaxation phase of the cardiac cycle ends with : *(AI 1998)*
   A. Peak of 'C' waves
   B. Opening of A.V. valve
   C. Closure of semilunar valve
   D. Beginning of 'T' wave

520. Cardiac index in a normal person is
   A. 2.1 *(TN 96, Kerala 95, KA 99, UP 02)*
   B. 3.2
   C. 4.6
   D. 5.9

521. Cardiac output in L/min divided by heart rate equals:
   A. Cardiac efficiency *(AI 1995)*
   B. Mean stroke volume
   C. Cardiac index
   D. Mean arterial pressure

522. Mean arterial pressure is : *(AI 1996)*
   A. Systolic + (Diastolic BP)/2
   B. Systolic + $1/3^{rd}$ Pulse pressure
   C. Diastolic + (Systolic BP)/2
   D. Diastolic + $1/3^{rd}$ Pulse pressure

523. Mean arterial pressure is calculated as:
   A. (SBP + 2DBP)/3 *(AIIMS Nov 06)*
   B. (DBP + 2SBP)/3
   C. (SBP + 3DBP)/2
   D. (DBP + 3SBP)/2

524. Blood pressure is defined as the product of:
   A. Systolic pressure × pulse *(PGI Dec 98)*
   B. Diastolic pressure × pulse rate
   C. Pulse pressure × pulse rate
   D. Cardiac output × peripheral resistance

525. SI unit for measuring Blood Pressure is: *(AI 02)*
   A. Torr
   B. mmHg
   C. $kP_a$
   D. Barr

526. The blood pressure measured by a sphygmomanometer
   A. Is lower than the intraarterial pressure *(AI 08)*
   B. Is higher than the intraarterial pressure
   C. Is same as the intraarterial pressure
   D. Is the same with different cuff sizes

527. True about blood pressure measurement is all/except:
   A. Cuff width should be 40% of arm circumference
   B. Diastolic blood pressure is indicated by fourth Korotkoff sound *(AIIMS May 07)*

C. Small cuff measures spuriously elevated Diastolic blood pressure
D. Monkenberg sclerosis causes pseudohypertension

528. Spuriously high BP is seen in A/E:
A. Auscultatory gap *(AIIMS May 01)*
B. Small cuff
C. Thick calcified vessels
D. Obesity

529. Which is true about measurement of BP with syphgnomonmeter versus intraarterial pressure measurements: *(AI 2001)*
A. Less than intravascular pressure
B. More than intravascular pressure
C. Equal to intravascular pressure
D. Depends upon blood flow

530. All of the following statements regarding subendocardial infarction are true, except: *(AI 06)*
A. These are multifocal in nature
B. These often result from hypotension or shock
C. Epicardities is not seen
D. These may result in aneurysm

531. A 45 year old male had severe chest pain and was admitted to the hospital with a diagnosis of acute Myocardial Infarction. Four days later he died and autopsy showed Transmural coagulative necrosis. Which of the following microscopic features will be seen on further examination *(AI 2009)*
A. Fibroblasts and collagen
B. Granulation tissue
C. Neutrophilic infiltration surrounding coagulative necrosis
D. Granulomatous inflammation.

532. A 60 year old male presented with acute chest pain of 4 hours duration. Electrocardiographic examination revealed new Q wave with ST segment depression. He suffered to his illness within 24 hours of admission. The heart revealed presence of a transmural hemorrhagic area over the septum and anterior wall of the left ventricle. Light microscopic examination is most likely to reveal: *(AI 04)*
A. Edema in between normal myofibrils
B. Necrotic myofibrils with presence of neutrophils
C. Coagulative necrosis of the myocytes with presence of granulation tissue
D. Infiltration by histiocytes with hemosiderin laden macrophages

533. A myocardial infarct showing early granulation tissue has most likely occurred: *(AI 02)*
A. 1 hours old
B. 24 hours old
C. 1 week old
D. 1 month old

534. Most common cause of aortic aneurysm is:
A. Syphilis *(AI 98)*
B. Marfan's syndrome
C. Atherosclerosis
D. Congenital

535. Most common cause of Abdominal aneurysm is:
A. Atherosclerosis *(AI 94)*
B. Trauma
C. Marfan's syndrome
D. Congenital

536. In Marfan's syndrome, Aortic aneurysm occurs most commonly in: *(AI 95)*
A. Ascending aorta
B. Descending aorta
C. Abdominal aorta
D. Arch or aorta

537. Clinical finding in AV fistula is one of the following:
A. Pericarditis *(AIIMS Nov 98)*
B. Sinus tachycardia
C. Cardiac arrhythmia
D. Hypothermia

538. In gram negative septicemia, early findings setting before shock of florid is: *(AI 99)*
A. Cardiac output, Total peripheral resistance
B. Cardiac output, Total peripheral resistance
C. Cardiac output, Total peripheral resistance
D. Cardiac output, Total peripheral resistance

539. A 70 year old man develops pneumonia and septicemia. Patient goes into renal failure and has a BP of 70/50 mm of Hg. Drug that should be used to maintain BP is: *(AI 07)*
A. Adrenaline
B. Ephedrine
C. Phenylephrine
D. Nor epinephrine

540. Renal failure in patients with septic shock occurs primarily from: *(NBE)*
A. Acute tubular necrosis
B. Acute cortical necrosis
C. Acute clomerulonephritis
D. Acute papillary damage

541. Which of the following statements is true about High Attitude Pulmonary Edema (HAPE)? *(AIIMS Nov. 06)*
A. Not exacerbated by exercise
B. Associated with pulmonary vasoconstriction
C. Occurs only in unacclamatized individuals
D. Associated with low cardiac output

542. During cardiac imaging the phase of minimum motion of heart is: *(AI 2010)*
A. Late systole
B. Mid systole
C. Late diastole
D. Mid diastole

543. Cardiovascular complications of HIV infection include all of the following, Except *(AI 2009)*
A. Pericardial Effusion
B. Cardiac Tamponade
C. Cardiomyopathy
D. Aortic Aneurysm

544. The most common cause of Left Ventricular Hypertrophy is: *(NBE)*
   A. Hypertension
   B. Aortic Stenosis
   C. Aortic Regurgitation
   D. HOCM

545. Investigation of choice to confirm Hemochromatosis as the cause of cardiomyopathy is : *(NBE)*
   A. ECG
   B. Echo
   C. MRI
   D. CT

546. Most common cardiovascular abnormality seen in Marfan's Syndrome on presentation is: *(NBE)*
   A. Mitral Valve Prolapse
   B. Dilation of Aortic Sinuses
   C. Coarctation of Aorta
   D. Bicuspid Aortic Valve

547. Most common complication of cardiac catheterization is: *(NBE)*
   A. Vascular Access Site Bleeding
   B. Arrhythmia
   C. Contrast reaction
   D. Perforation of heart chamber

548. Osborne waves in ECG are seen in : *(NBE)*
   A. Hypothyroidism
   B. Hypothermia
   C. Hypocalcemia
   D. Hypokalemia

549. Epsilon wave is seen in: move *(NBE)*
   A. Brugada syndrome
   B. Hypothermia
   C. WPW syndrome
   D. Arrhythmogenic right ventricular dysplasia

550. The most important modifiable risk factor for Stroke is: *(NBE)*
   A. Hyperlipidemia
   B. Diabetes mellitus
   C. Cigarette Smoking
   D. Hypertension

551. Transesophageal echocardiogram (TEE) is preferred to Trans-thoracic echocardiogram (TTE) in:
   A. Evaluation of Pericardial diseases *(AIIMS 2013)*
   B. Evaluation of Tricuspid wall vegetations
   C. Evaluation of Left Ventricular Apical Thrombi
   D. Evaluation of Left Atrial Appendage Thrombi

552. Idiopathic degeneration of the proximal bundle branch fibres is known as: *(AIIMS 2013)*
   A. Lev's Disease
   B. Lenegre's Disease
   C. Ashman Phenomenon
   D. Brugada Syndrome

553. All of the following conditions are more commonly associated with LBBB pattern than RBBB Pattern on ECG, Except: *(AIIMS 2013)*
   A. Acute MI
   B. Aortic valve disease
   C. Lev Disease
   D. Ashman Phenomenon

554. Brugada Syndrome is associated with: *(AIIMS 2013)*
   A. Left Bundle Branch Block
   B. Left Anterior Fascicular block
   C. Left Posterior Fascicular block
   D. Right Bundle Branch Block

## ANSWERS, REFERENCES, EXPLANATIONS AND RELEVANT HIGH YIELD FACTS

### Arterial Pulses

#### Pulsus Bisferiens

**1. Answer is D (Tetralogy of Fallot):** *Harrison 18th/p 1824 Harrisons 17th / 1383, 1384; Harrisons 16th /1305; Hurst's 12th/ 245*

***Pulsus Bisferiens is not associated with Tetralogy of fallot.***

**Pulsus Bisfenens**

| Characteristic Causes (Harrisons) | Other causes (Hurst) |
|---|---|
| • ***Aortic Refurgitation (AR)*** Q<br>• ***Aortic Regurgitation with Aortic Stenosis (AR+AS)*** Q<br>• ***Hypertrophic Cardiomyopathy*** Q | Condition associated with rapid election of an increased stroke volume from the left ventricle<br>• *Exercise*<br>• *Fever*<br>• *PDA* |

| Pulses alternans Q | Bisferiens pulse Q | Pulsus paradoxus Q | Dicrotic pulse Q |
|---|---|---|---|
| • Regular alteration of pressure in pulse with regular rhythm (single peak)<br>• Seen in<br>- LVF Q<br>- may be seen in all conditions leading to LVF | • Two systolic peaks<br>• Seen in<br>- Aortic regurgitation Q ± AS<br>- Hypertrophic cardiomyopathy Q | • Normal decrease in systolic pressure during inspiration is accentuated Q<br>• Seen in<br>- Pericardial tamponade Q<br>- S.V.C. obstruction Q<br>- COPD/Acute Severe Asthma<br>- Constrictive pericarditis<br>- Pulmonary embolism<br>- Hypovolemic shock | • Has two palpable waves are in systole and one in diastole.<br>• Seen in<br>- dilated cardiomyopathy |

**2. Answer is D (TOF):** *Refer previous question*

***Aortic Regurgitation alone or with Aortic stenosis and Hypertrophic cardiomyopathy are all associated with pulsus bisferiens***

**3. Answer is C (Radial artery):** *Harrison 18th/p 1824, 1825 Harrison 15th/ 1255, Harrison 16th/ 1305; Harrison 17th/1383, 1384*

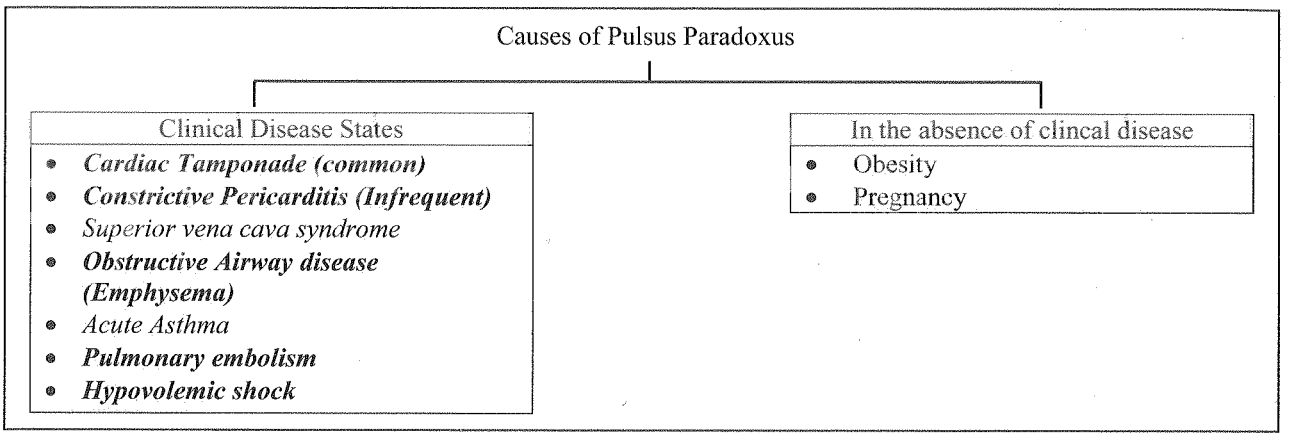
*Usually palpation of peripheral arterial pulses such as radial artery gives less information than examination of a more central pulse (Carotid pulse) regarding alterations in left ventricular ejection or Aortic valve function. However certain findings such as **Bisferiens pulse of Aortic regurgitation or pulses alternans are more evident in peripheral arteries.** – Harrison*

#### Pulsus Paradoxus

**4. Answer is A (IPPV):** *Harrison 18th/p 1824, 1825 Harrison 15th/ 1255, Harrison 16th/ 1305; Harrison 17th/ 1384*

***Pulsus paradoxus is not a feature of IPPV.***

*Pulsus paradoxus may be seen in association with cardiac tamponade, constrictive pericarditis (infrequent) and COPD.*




**What is Pulsus Paradoxus**

*Normally the arterial pulse volume and arterial blood pressure decreases during inspiration and increases during expiration.*

***Pulsus paradoxus*** is an aggravation of a normal process and hence also called *pulses normalis aggregans.*

In pulses paradoxus the decrease in systolic arterial pressure during inspiration is accentuated.

*What then in the paradox*:

In patients with pericardial tamponade, airway obstruction or superior vena caval obstruction, the decrease in systolic arterial pressure may be so much that the peripheral pulse may completely disappear during inspiration.

*The paradox is that the heart sounds may still be heard on auscultation over the apex at a time when no pulse is palpable at the radial artery.*

5. **Answer is D (Hypertrophic cardiomyopathy):** *Harrison 18th/p 1824, 1825, 1975 Harrisons 17th/1384; 1491: Hurst 12th/241, 242, 245, 246 Braunwold 8th/133*

*Pulsus paradoxus is not a feature of Hypertrophic cardiomyopathy.*
*Pulsus paradoxus may be associated with chronic obstructive pulmonary disease (emphysema), pulmonary embolism and Hypovolemic shock.*

6. **Answer is C (Seen in constrictive pericarditis):** Harrison 18th/p 1975 *Harrisons 17th/1491*

*Pulsus Paradoxus may be seen in constrictive pericarditis*
*'Pulsus paradoxus is charachteristic of cardiac tamponade but is also seen in about one- third of patients with constrictive pericarditis' - Harrisons*

7. **Answer is A (Cardiac tamponade); B (Constrictive pericarditis); & E (Severe asthma):** Harrison 18th/p 1824, 1975 *Harrisons 17th/1384, 1491, Hurzt 12th/241, 242, 245, 246, Braunwald 8th/133*

***Pulsus paradoxus is characteristic of cardiac tamponade but also seen in constrictive pericarditis and acute asthma***

## Pulsus alternans

8. **Answer is D (MI):** *Harrison 18th/p 1825 Harrisons 17th/1384, Hurst 12th/241*

***Pulsus alternans indicates severe impairment in LV function and may be seen in conditions causing severe LV dysfunction such as Myocardial Infarction***

**Pulsus Alternans**

- Pulsus alterans is charachterized by regular alteration of the pressure pulse amplitude despite a regular rhythm
- It is defined by beat to beat variation of the pulse amplitude but with a single peak and independent of the respiratory cycle.

| |
|---|
| In pulsus bigeminus there is also a regular beat to beat variation but it is caused by a premature ventricular contraction that follows each regular beat |

- Pulsus alterans is charachteristically seen in Left ventricular failure and conditions causes LVF (including MI)

Causes of Pulsus Alternans

| In patients with Heart Disease | In patients without Heart Diesease |
|---|---|
| • Left ventricular Failure and conditions causing LVF | • During or following paroxysmal tachycardia<br>• For several beats following a premature beat |

*Presence of pulsus alterans usually indicates severe impairment of LV function.*

## Pulsus Bigeminus

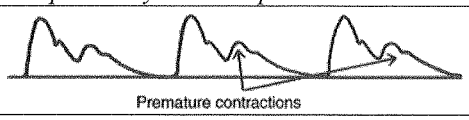
**9. Answer is C (Compensatory pause is absent):** *Refer text below*

***Pulsus Bigeminus is associated with a compensatory Pause. Compensatory pause is absent in Pulsus Alternans***

*Pulsus Bigeminus is a disorder of rhythm (Irregular rhythm) caused by a normal beat alternating with a premature contraction and a compensatory pause resulting in alternation of the strength of pulse. The stroke volume of the premature beat is diminished in relation to that of the normal beats, and the pulse varies in amplitude accordingly. Pulsus Bigeminus most closely mimics Pulsus Alternans from which it must be distinguished. In Pulsus Alternans the rhythm is regular and the compensatory pause is absent.*

| Causes of Bigeminus Pulse |
|---|
| • Extrasystole/Premature contractions : *Digitalis Toxicity (Pulsus Bigeminus is as sign of digitalis toxicity)*<br>• Heart Block *(SA or AV Block with a 3:2 conduction ratio)*<br>• Sick Sinus Syndrome (Here a junctional escape followed by sinus capture produces an escape capture Bigeminus rhythm) |

| *Pulsus Alternans* |
|---|
| *The pulse alternates in amplitude (pressure) from beat to beat* |
| *Rhythm is regular*<br>*Every beat comes after the same interval but every alternate beat is weaker than the other* |
| *No Compensatory Pause* |
| |
| *A weak contraction decreases the ejection fraction hence increasing the end-diastolic volume (the volume of blood remaining in the ventricle). As a result, in the next cardiac cycle the heart generate higher pressures (Frank-Sterling Mechanism) and a stronger pulse is perceived. There is no compensatory pause and hence the rhythm remains regular* |

| *Pulsus Bigeminus* |
|---|
| *The pulse alternates in amplitude (pressure) from beat to beat* |
| *Rhythm is irregular*<br>*Every beat does not come at the same interval but every alternate beat is weaker than the other* |
| *Compensatory Pause is present* |
|  |
| *The premature contraction leads to a weak pulse and is followed by a compensatory pause. The pulse following the compensatory pause is typically stronger.Stronger pulse is due to more diastolic filling following long compensatory pause (Frank-Sterling Mechanism) and extrasystolic potentiation of ventricular contraction. Since there is a compensatory pause, the rhythm becomes irregular* |

**10. Answer is A (Digitalis):** *Clinical Diagnosis For Medical Undergraduates, 2ND/ 134; Approach to Practical Paediatrics 2nd/ 122*

***Pulsus Bigeminus is recognized as a cause of digitalis toxicity.***

*Pulsus Bigeminus is a disorder of rhythm (Irregular rhythm; arrhythmia) most commonly caused by Premature Ventricular Contractions that results in a pulse with irregular rhythm that alternates in amplitude (pressure) from beat to beat. The most common cause of Pulsus Bigeminus is Digitalis and Pulsus Bigeminus is recognized as a cause of digitalis toxicity.*

## Miscellaneous Pulses

**11. Answer is B (Aortic Regurgitation ):** Harrison 18th/p 1943, 1944 *Harrisons 17th/1476*

*The Water hammer pulse or Corrigan's pulse is characterized by an abrupt and rapid carotid upstroke with a rapid fall off (collapsing pulse). It is characteristic of Aortic Regurgitation.*

**12. Answer is C (A.S):** Harrison 18th/p 1939 *Harrisons 17th/1473*

*Double Apical Impulse may be seen in Aortic Stenosis and Hypertrophic obstructive cardiomyopathy (HOCM)*

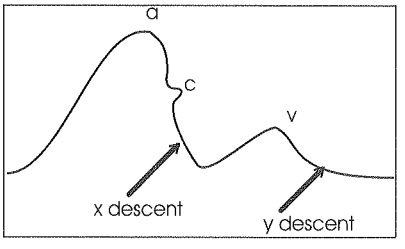
| Double Apical Impulse |
|---|
| • *Aortic Stenosis*[Q] |
| • *HOCM*[Q] |

## Jugular Venous Pulse (JVP)

**13. Answer is A (c wave – onset of atrial systole):** Harrison 18th/p 1823 *Harrison 15th/ 1256, Harrison 16th/ 1305, 1306; 17th/ 1384*

*Onset of atrial systole is marked by production of a waves on JVP and not by c waves.*

**Jugular venous pulse : Review**




| | | |
|---|---|---|
| **a waves :** | Due to distention produced by rt. atrial contraction. | |
| **c waves :** | Are positive waves produced by bulging of tricuspid valve into right atrium during right ventricular isovolumetric contraction. | |
| **v waves:** | Due to increasing volume of blood in the right atrium during ventricular systole when the tricuspid valve is closed. | |
| **a – x descent:** | Due both to atrial relaxation and to the downward displacement of the tricuspid valve during ventricular systole. | |
| | Accentuated in | Reduced with |
| | - Constrictive pericarditis<br>- Cardiac temponade<br>- Restrictive cardiomyopathy | - Right ventricular dilatation<br>Reversed with<br>- Tricuspid Regurgitation |
| **v – y descent:** | By the opening of the tricuspid valve and the subsequent rapid inflow of blood into the right ventricle. | |
| | Accentuated in | Reduced with |
| | - Tricuspid regurgitation<br>- Constrictive pericarditis | - Tricuspid stenosis<br>- Right / Atrial Myxoma (Suggests obstruction to right ventricular filling) |
| **y – a descent:** | Due to continuous diastolic inflow of blood into great veins, right atrium and ventricle which are all in free communication during diastole. | |

**14. Answer is A (Cannon waves in complete heart block):** *Harrison 14th/ 1232-34, Harrison 15th/ 1256, Harrison 16th/ 1305, 1306; Harrison 17th/ 1384*

*Cannon a waves are large 'a' waves that may be seen in complete heart block.*

- **Cannon waves are large 'a' waves. They may be seen in complete heart block.**
- **Slow v-y descent** in the JVP suggests an obstruction to right ventricular filling, as occurs with Tricuspid Stenosis or Right Atrial Myxoma.
  **Tricuspid Regurgitation** causes the v-waves to be prominent, when TR becomes severe, the combination of a prominent v-wave and obliteration of x-descent results in a single large positive systolic wave.
- **Tricuspid stenosis is associated with large/giant 'a' waves and not large/giant c waves.**
  **Tricuspid stenosis**- Positive presystolic a-wave is enlarged when the right atrium is contracting against an increased resistance.
- **SVC obstruction** causes raised JVP with absent pulsation (OHCM 5th/ 78)

| Raised JVP ċ normal wave form | Raised JVP ċ absent pulsation |
|---|---|
| Fluid overload / Right heart failure | SVC obstruction |



15. **Answer is C (Tricuspid Regurgitation):** Harrison 18th/p 1823 *Harrison 15th/ 1256, 1257, Harrison 16th/ 1306; Harrison 17th/ 1384*

*Tricuspid stenosis (not Tricuspid regurgitation) is associated with large or 'a' giant waves.*

**'a' waves in JVP:**
*Are positive waves, due to distension produced by Right atrial contraction.*
*Large 'a' waves indicate atrium is contracting against increased resistance.*

| Large 'a' waves : | Cannon 'a' waves : | Absent 'a' waves : |
|---|---|---|
| • ***Tricuspid stenosis*** Q<br>• Pulmonary stenosis Q<br>• ***Pulmonary hypertension*** Q | • Regularly<br>- During ***junctional rhythm*** Q<br>• Irregularly<br>- Atrioventricular dissociation with ventricular tachycardia<br>- *Complete heart block* Q | *Atrial fibrillation* Q |

16. **Answer is A (Atrial fibrillation):** *Harrison 18th/p 1823 Harrison 15th/ 1256, 1257, Harrison 16th/ 1306; Harrison 17th/ 1384*
*Absent 'a' waves are characteristic of atrial fibrillation.*

17. **Answer is B (Tricuspid valve bulging into right atrium):** Harrison 18th/p 1823 *Harrisons 17th /1384; Harrisons 16th/1305*

*The 'C' Wave is a positive wave produced by the bulging of tricuspid valve into the right atrium during right Ventricular isovolumetric systole and by impact of the carotid artery adjacent to the jugular vein. -Harrisons 17th /1384*

18. **Answer is B (Bulging of Tricuspid valve):** Harrison 18th/p 1823 *Harrison 17th/1384; Repeat*

*The 'c' wave in JVP is a positive wave produced by the bulging of the tricuspid valve into the right atrium during right ventricular isovolumetric systole and by the impact of the carotid artery adjacent to the jugular vein.*

19. **Answer is A (Absent Y descent):** *Harrison 18th/ 1972; Harrisons 17th/1490*

*Cardiac tamponade is charachterized by jugular venous distension (↑ ed JVP) with a prominent X descent but an absent Y descent - Harrisons*

| Feature | Tamponade | Constrictive pericarditis | Restrictive cordiomyopathy | RVMI |
|---|---|---|---|---|
| ***Prominent y descent*** | ***Absent*** | Usually present | Rare | *Rare* |
| ***Prominent x descent*** | Present | Usually present | Present | *Rare* |

## Pulse Pressure

**20. Answer is C (Systolic – Diastolic B.P):** *Ganong 21st / 589*

*Pulse pressure is the difference between the systolic pressure and the diastolic pressure.*

**21. Answer is D (Congestive Heart Failure):** *CPDT 16th/547*

*Congestive Heart Failure is associated with a narrow pulse pressure*

**Pulse Pressure**

Pulse pressure is the difference between systolic and diastolic blood pressure

| Wide pulse pressure (>50% systolic BP) | Narrow Pulse Pressure (<25% systolic BP) |
|---|---|
| **Common Causes** | **Common causes** |
| • *Aortic Regurgitation*<br>• *Patent Ductus Arteriosus*<br>• *Complete Heart Block*<br>• *Hyperthyroidism*<br>• *Beri Beri*<br>• *Pregnancy*<br>• *Fever /Hot weather*<br>• *Anemia*<br>• *Anxiety*<br>• *Paget's disease of bone (Extensive AV shunting through bone)*<br>• *Arteriovenous shunting*<br>• *Others (Life threatening increased ICP etc)* | • *Congestive Heart Failure*<br>• *Aortic stenosis (severe)*<br>• *Cardioc Tamponade*<br>• *Dehydration* |

**22. Answer is B (Aortic Stenosis):** *Refer previous question*

*Aortic Stenosis is associated with a narrow pulse pressure.*
*Patent Ductus Arteriosus (PDA), Aortic Regurgitation and AV Malformations (Arteriovenous shunting) are all associated with a wide pulse pressure.*

## Pulse Deficit

**23. Answer is C (Atrial Fibrillation):** *Clinical Diagnosis Cardiovascular System By Rajenderan (Jaypee Brothers Publishers) 2ND/ 47; Clinical Examination: A Practical Guide in Medicine By Hira Harmanjit Singh (JP Medical Ltd) 2011/ 139; Clinical Examination In Cardiology By Rao (Elsevier India) 2007/ 232; Sapira's Art & Science of Bedside Diagnosis (Lippincott Williams & Wilkins, 2010) 4th/ 105*

*Atrial Fibrillation is the most common cause of Pulse Deficit and the pulse deficit is often more than 10 per minute.*

***Pulse deficit refers to the difference between the radial pulse rate and the heart rate counted by auscultation (Apical Ventricular Rate).*** *Pulse deficit is produced when ventricular contractions are preceded by short diastoles such that poor ventricular filling results in insufficient stroke volume to transmit the pressure wave out to the radial pulse. The radial pulse rate is always lower than the ventricular pulse rate.*

*The most common cause of pulse deficit is atrial fibrillation and pulse deficit has traditionally been believed to be a classical bedside sign for diagnosis of atrial fibrillation. Pulse deficit may however be produced by any*

*tachyarrhythmia (fast heart rate) or Extra-systoles (Premature Ventricular Contractions).* ***Typically Pulse deficits generated by Multifocal PVC or PAC are small (<10/min) while those generated by Atrial Fibrillation are larger (>10/ min). Pulse deficits of more than 10 per minute are frequent in Atrial Fibrillation with a fast heart rate.***

| *Major Causes of Pulse Deficit (Tachyarrhythmias)* |
|---|
| • ***Atrial fibrillation*** |
| • ***Premature Ventricular Contraction*** |

**Differentiating clinical features between VPCs and AFP**

| Features | VPCs | AF |
|---|---|---|
| Pulse deficit | <10/min | >10/min |
| 'a' wave in JVP | Present | Absent |
| Effect of exertion | Decrease or disappear | Persists or increases |
| Rhythm | Short pause (between normal beat and VPC) followed by a long pause (following VPC) | Pauses are variable and c wave chaotic |

***Note : Multifocal Premature atrial contractions (PAC) may also produce small pulse deficits.***

**24. Answer is B (Bradyarrhythmias)**

*Pulse deficits are seen in Tachyarrhythmias and not in Bradyarrhythmias.*

*Pulse deficit refers to the difference between the radial pulse rate and the heart rate counted by auscultation (Apical Ventricular Rate). Pulse deficit is produced when ventricular contractions are preceded by short diastoles such that poor ventricular filling results in insufficient stroke volume to transmit the pressure wave out to the radial pulse. The radial pulse rate is always lower than the ventricular pulse rate. The most common cause of pulse deficit is atrial fibrillation and pulse deficit has traditionally been believed to be a classical bedside sign for diagnosis of atrial fibrillation.* ***Pulse deficit may however be produced by any tachyarrhythmia (fast heart rate) or Extra-systoles (Premature Ventricular Contractions). Multifocal Premature atrial contractions (PAC) may also produce small pulse deficits.***

| Major Causes of Pulse Deficit (Tachyarrhythmias) |
|---|
| • ***Atrial fibrillation*** |
| • ***Premature Ventricular Contraction*** |
| • ***Premature Atrial Contractions (May be seen)*** |

*Typically Pulse deficits generated by Multifocal PVC or PAC are small (<10/min) while those generated by Atrial Fibrillation are larger (>10). Pulse deficits of more than 10 per minute are frequent in Atrial Fibrillation with a fast heart rate.*

**25. Answer is D (Radial pulse rate may be more than ventricular pulse rate):** *Clinical Diagnosis Cardiovascular System By Rajenderan (Jaypee Brothers Publishers) 2ND/ 47; Clinical Examination: A Practical Guide in Medicine By Hira Harmanjit Singh (JP Medical Ltd) 2011/ 139; Clinical Examination In Cardiology By Rao (Elsevier India) 2007/ 232; Sapira's Art & Science of Bedside Diagnosis (Lippincott Williams & Wilkins, 2010) 4th/ 105*

***The radial pulse rate is always lower than the ventricular pulse rate.***

*Pulse deficit refers to the difference between the radial pulse rate and the heart rate counted by auscultation (Apical Ventricular Rate). Pulse deficit is produced when ventricular contractions are preceded by short diastoles such that poor ventricular filling results in insufficient stroke volume to transmit the pressure wave out to the radial pulse. The radial pulse rate is always lower than the ventricular pulse rate.*

| Pulse Deficit in Atrial Fibrillation |
|---|
| • *Atrial fibrillation is the most common cause of pulse deficit* (Pulse deficit has traditionally been believed to be a classical bedside sign for diagnosis of atrial fibrillation) |
| • *Pulse deficit in Atrial Fibrillation is often more than 10 per minute.* |
| • ***Pulse deficit in atrial fibrillation is greater when the ventricular rate is high*** |
| • ***Pulse deficit in atrial fibrillation may be absent in patients with slow ventricular rate (<50)*** |
| • *If a digitalized patient with a prior diagnosis of chronic atrial fibrillation presents with a perfectly regular pulse, one should suspect digitalis intoxication with a regular nodal rhythm and atrioventricular dissociation.* ***(Note that in this form of 'regularized' atrial fibrillation, the apical- radial pulse deficit also disappears.)*** |

## Cardiac Auscultation: Heart Sounds and Murmurs

### General

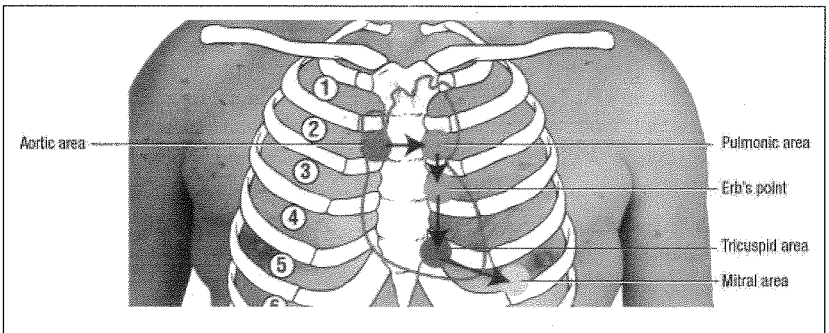
**26. Answer is C (Right 3rd intercostal space):** *Auscultation Skills: Breath & Heart Sounds (Lippincott Williams & Wilkins 4th (2009)/ 198,201; Chamberlain's Symptoms and Signs in Clinical Medicine 13th/ 56; Evaluating Heart and Breath Sounds (Lippincott Williams & Wilkins) 2009/62*

*In cardiology, Erb's point refers to the third intercostal space on the left sternal border where both components of S2 (A2 and P2) can be well appreciated.*

*Both components of S2 (A2 and P2) are usually well transmitted to the Erb's point. The physiological splitting of S2 into A2 and P2 is believed to be appreciated best at the Erb's point or in the pulmonic area.*

- *A2 is best heard over the aortic area in the right second intercostal space*
- *P2 is best heard over the pulmonic area in the left second intercostal space*
- *Second heart sound (S2) is best heard over the pulmonic area (Since both A2 and P2 can be heard at the pulmonic area) and at the Erb's Point. Note that even at the pulmonic area A2 is louder than P2*

| | | |
|---|---|---|
| 1 | Aortic area | Second intercostal space to the right of the sternum (along right upper sternal border) |
| 2 | Pulmonic area | Second intercostal space to the left of the sternum (along left upper sternal border) |
| 3 | Erb's point | Third intercostal to the left of the sternum(along left sternal border) |
| 4 | Tricuspid area | Fourth or Fifth intercostal space to the left of the sternum (along left lower sternal border) |
| 5 | Mitral area (Apex) | Fifth intercostal space on the left midclavicular line. |




**27. Answer is A (3rd left intercostal space):** *Auscultation Skills: Breath & Heart Sounds (Lippincott Williams & Wilkins 4th (2009)/ 198,201; Chamberlain's Symptoms and Signs in Clinical Medicine 13th/ 56; Evaluating Heart and Breath Sounds (Lippincott Williams & Wilkins) 2009/62*

*Best areas to auscultate for both components of the second heart sound (A2 and P2 ) are either the left sternal border at the level of second intercostal space (Pulmonic area) or the left sternal border at the level of third intercostal space (Erb's point).*

*The second heart sound has two components A2 (from Aortic closure) and P2 (from pulmonary closure). P2 is a soft sound that is poorly transmitted. It is best heard at the pulmonic area and is transmitted only as far as the Erb's point. A2 is a loud sound best heard over the aortic area but since it is widely transmitted it may be heard across all areas of the chest even as far as the apex. Second heart sound (S2) is best heard over the pulmonic area (Since both A2 and P2 can be heard at the pulmonic area). Note that even at the pulmonic area A2 is louder than P2. The other area to auscultate for both components of the second heart sound is at the left sternal border of the third intercostal space (Erb's point)*

**28. Answer is A (2nd left intercostal space):** *Auscultation Skills: Breath & Heart Sounds (Lippincott Williams & Wilkins 4th (2009)/ 198,201; Chamberlain's Symptoms and Signs in Clinical Medicine 13th/ 56; Evaluating Heart and Breath Sounds (Lippincott Williams & Wilkins) 2009/62*

*The pulmonary component (P2) of the Second Heart sound (S2) is best heard over the Pulmonary Area located at the second intercostal space to the left of the sternum (along left sternal border).*

- *A2 is best heard over the aortic area in the right second intercostal space*
- *P2 is best heard over the pulmonic area in the left second intercostal space*
  - *Second heart sound (S2) is best heard over the pulmonic area (Since both A2 and P2 can be heard at the pulmonic area) and at the Erb's Point. Note that even at the pulmonic area A2 is louder than P2*

## First Heart Sound (S1)

**29. Answer is C (Heard at the end of ventricular systole):** *Refer text below*

*S1 is heard at the start of ventricular systole and not at the end.*

*S1 has a lower frequency (25-45 Hz) than S2 (50 Hz). It is caused by closure of mitral and tricuspid valves and is heard well with the diaphragm of stethoscope.*

**Heart Sounds :Review**

| Feature | 1st heart sound | 2nd heart sound | 3rd heat sound | 4th heart sound |
|---|---|---|---|---|
| Character | High pitched (lower than $S_2$) Slightly prolonged "lub" | High pitched (higher than $S_1$) Shorter "dup" | Soft low pitched weak rumbling | Low pitched heart sound |
| Duration | 0.14 second | 0.11 sec | 0.1 sec | - |
| Frequency | 25-45 Hz | 50 Hz | - | ***< 20 Hz*** $^{Q}$ |
| Cause | Sudden closure of mitral & tricuspid valves | Closure of aortic & pulmonary valves | ***Rapid ventricular filling*** $^{Q}$ d/t inthrushing of blood from atria | ***Ventricular filling*** $^{Q}$ d/t atrial contraction causing inthrushing of blood |
| Timing | Start of ventricular systole | Just after end of ventricular systole | Begining of middle third of diastole | Immediately before 1st heart sound (presystolic) |
| Heard | Better heard with Diaphram | Better heard with Diaphram | ***Better heard with the Bell*** | ***Better heard with the Bell*** |

***$S_3$ & $S_4$ can often not be heard with a stethoscope (ear)*** $^{Q}$ and requirw phonocardiogram
$S_3$ often and $S_4$ sometimes can be recorded in phonocardiorgam

*The first and second heart sounds and opening snaps are heard better with the diaphragm, and low-pitched sounds such as the third or fourth heart sound are beter heard with the bell of stethoscope – Hutchisons 20th/ 174*

**30. Answer is A (Short PR interval):** Harrison 18th/p 1827 *Harrison 15th/ 1258, Harrison 16th/ 1307; Harrison 17th/ 1385*

*Short PR interval is associated with a Loud $S_1$.*
*$S_1$ is produced as a result of closure of AV valves.*
*In short PR interval mitral leaflets are at a greater distance from neutral as decreased interval between atrial contraction and ventricular systole does not allow them to return towards neutral before the ventricular contraction arrives. This results in a louder $S_1$*

**Causes of Soft S1**

| Poor conductance of sound through chest wall | Decrease in rate of LV pressure development | PR interval and velocity of valve closure | Mobility of valve |
|---|---|---|---|
| • ***Obesity*** | • Myxoedema | • *Prolonged PR interval eg 1st degree heart block* | ***Severe calcification of valve or reduced mobility of valve is associated with soft S1.*** |
| • *Emphysema* | • *Cardiomyopathy* | | *Long standing mitral stenosis is associated with severe calcification of mitral valve and soft S1.* |
| • ***Pleural effusion*** | • *Acute MI* | | |
| • *Pericardial effusion* | • ***Mitral regurgitation*** | | |

**31. Answer is E (All of the above):** Harrison 18th/p 1826 *Harrison 17th/1385; Hurst 12th/261*

*Long standing severe M.S. (calcified mitral valve), obesity, mitral regurgitation and pleural effusions are all established causes of soft S1.*

**Factors that determine the intensity of $S_1$**

**Intensity of $S_1$ depends on**

- Position of mitral leaflets at the onset of ventricular systole
  - Mitral leaflets at a greater distance than normal ***(Short PR interval)*** → Loud $S_1$ ♀
  - Mitral leaflets at a lesser distance than normal ***(Long PR interval)*** → Soft $S_1$ ♀
- Rate of rise of left ventricular pressure pulse.
  - Low rate of rise of pressure ***(VSD♀/ MR♀)*** → Soft $S_1$ ♀
  - High rate of rise of pressure ***(AS)♀*** → Loud $S_1$ ♀
- Presence or absence of structural disease of mitral disease
  - IMMOBILE mitral leaflet as with ***calcification in MS*** → Soft $S_1$
- Amount of tissue, air or fluid between heart and stethoscope
  - Greater tissue (Obesity) → Soft $S_1$

**32. Answer is C (Short PR interval) and D (Tachycardia):** Harrison 18th/826; *Harrison 17th 1385; Hurst 12th/260, 261*

*Short PR interval and Tachycardia are associated with Loud S1.*

**Causes of Loud S1**

**Tachycardia**

*S1 is louder if diastole is shortened due to tachycardia*
- Anemia
- Anxiety
- Fever

**Increased / Prolonged AV Flow**

**Increased AV Flow**

| Increased AV Flow due to High Cardiac output | Increased AV flow due to Left to Right shunting |
|---|---|
| • Thyrotoxicosis<br>• AV fistula | • ASD<br>• PDA<br>• Other conditions |

**Prolonged AV Flow**

Because of prolongation of AV flow due to stenosis
- Mitral stenosis
- Tricuspid stenosis

**Short PR interval (Velocity of valve closure)**

At short PR intervals the mitral valve leaflets are maximally separated by atrial contraction. At the onset of LV systole the mitral valve leaflets therefore close with a high velocity and with a large excursion resulting in loud S1.

**33. Answer is A (Prolonged flow through mitral valve):** Harrison 18th/p 1826 *Harrison 17th/1385; Hurst 12th/260, 261;*

*Refer previous question*

*Loud S1 in mitral stenosis results from prolonged AV flow through the mitral valve.*

*'S1 is louder if AV flow is prolonged because of mitral stenosis'* – Harrison
*Reduced mobility of valve (Immobility, calcification), and Prolonged PR interval (1st degree block) are all causes of soft S1.*

**Note:**
*First degree block is characterized by prolonged PR interval.*

**34. Answer is B (LBBB) and E (Atrial myxoma):** Harrison 18th/p 1826 *Harrison's 17th/1385; Hurst's 10th/244, 242*

*Left Bundle Branch Block, and Atrial myxoma are causes of reverse splitting of First Heart Sound (S1).*

First heart Sound (S1) and Splitting
- First heart sound (M1T1) is produced by closure of Mitral valve (M1) and closure of Tricuspid valve (T1)

- The mitral valve closes slightly before the Tricuspid valve (M1 → T1)
  This normal splitting (physiological splitting) cannot be detected by auscultation because both components are low pitched and separated only by 20-30 ms.
- Therefore splitting of first heart sound, whenever audible is considered pathological.

Pathological Split $S_1$

| Normal splitting<br>(T1 follows M1 after a longer gap : M1 T1) | Reverse splitting<br>(T1 precedes M1 : T1 M1) |
|---|---|
| • Right Bundle Branch Block<br>• LV pacing<br>• Ectopic beats and Idioventricular rhythms originating in Left Ventricle<br>• Ebstein's anomaly | • ***Left Bundle Branch Block***<br>• RV pacing<br>• Ectopic beats and Idioventricular rhythms originating in Right ventricle<br>• ***Severe Mitral Stenosis and Atrial Myxoma*** |



## Second Heart Sound

**35. Answer is C >A (ASD > VSD):** Harrison 18th/p 1826 *Hurst's 12th / 266, 268; Harrisons 17th/ 1385*

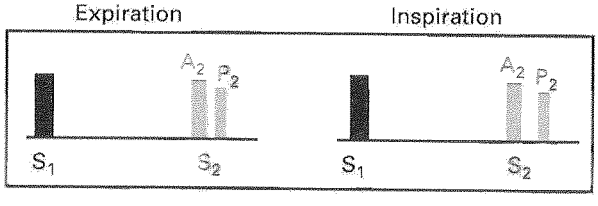
*Wide physiological splitting may be seen in both VSD and ASD but it is more characteristic of ASD. ASD is the single best anterior of choice.*

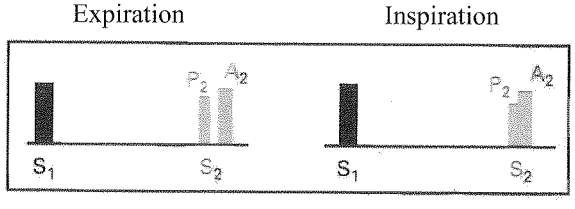
***Classic wide fixed splitting of S2 is found in patients with ASD'*** – *Hurst*

**Abnormal Expiratory Splitting of S2**
***(Audible splitting during expiration is considered Abnormal)***

Audible splitting during both expiration and inspiration

| • Wide physiological splitting<br>• This is caused by delayed P2/early A2 | • Reversed Splitting<br>• This is caused by delayed A2/early P2 |
|---|---|




*This is associated with Paradoxical movements i.e. P2 moves towards A2 with inspiration and hence splitting interval narrows with inspiration.*

| **Wide Physiologic Splitting of the second Heart Sound** |
|---|
| **Delayed pulmonic closure** |
| • Delayed electrical activation of the right ventricle<br>- Complete RBBB (proximal type)<br>- Left ventricular paced beats<br>- Left ventricular ectopic beats |
| • Prolonged right ventricular mechanical systole<br>- Acute massive pulmonary embolus<br>- Pulmonary hypertension with right heart failure<br>- Pulmonic stenosis with intact septum (moderate to severe) |

| **Reversed Splitting of the second Heart Sound** |
|---|
| **Delayed aortic closure** |
| • Delayed electrical activation of the left ventricle<br>- Complete LBBB (proximal type)<br>- Right ventricular paced beat<br>- Right ventricular ectopic beats |
| • Prolonged left ventricular mechanical systole<br>- Complete LBBB (peripheral type)<br>- Left ventricular outflow tract obstruction<br>- Hypertensive cardiovascular disease<br>- Arteriosclerotic heart disease<br>- Chronic ischemic heart disease<br>- Angina pectoris |

- Decreased impedence of the pulmonary vascular bed (increased hangout)
  - Normotensive atrial septal defect
  - Idiopathic dilation of the pulmonary artery
  - Pulmonic stenosis (mild)
  - ***Atrial septal defect***
  - Unexplained AES in normal subjects

**Early aortic closure**

- Shortened LVET
  - ***Mitral regurgitation***
  - ***Ventricular septal defect***

- Decreased impedance of the systemic vascular bed (increased hangout)
  - Poststenotic dilation of the aorta secondary to aortic stenosis or regurgitation
  - Patent ductus arteriosus

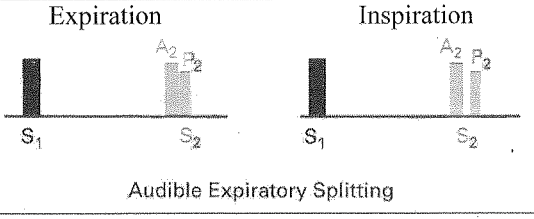
**Early pulmonic closure**

- Early electrical activation of the right ventricle
  - Wolff-Parkinson-White syndrome, type B

**Normal Physiological Splitting**

No audible splitting on Expiration; Audible splitting present on Inspiration.

- During expiration the Aortic sound (A2) and pulmonic sound (P2) are separated by less than 30 ms and are appreciated as a single sound
- During inspiration the splitting interval widens and A2 and P2 are clearly separated into two distinctly audible sounds.



Audible Expiratory Splitting

***Note: Audible splitting during expiration is considered Abnormal***

**36. Answer is C (LBBB):** *Refer Notes on Abnormal Splitting of S2*

*Left Bundle Branch Block (LBBB) is typically associated with Reversed or Paradoxical Splitting of S2*

*Paradoxical splitting of second heart sound is caused by delayed A2 or early P2. Left Bundle Branch Block (LBBB) is associated with delayed Aortic closure (delayed A2) due to delayed electrical activation of the left ventricle.*

*ASD and RBBB are associated with a wide physiological (non-paradoxical) split of second heart sound due to delayed pulmonic closure (Delayed P2) while VSD is associated with a wide physiological (non-paradoxical) split second heart sound from early aortic closure (Early A2).*

**37. Answer is A, E (ASD, Pulmonary Stenosis):** *Hurst 12th/268*

*ASD and pulmonic stenosis are associated with wide splitting of second heart sound due to associated delayed closure of pulmonic valve.*

**38. Answer is A, B, D (ASD, MR, PS):** *Hurst 12th/268*

*ASD and PS are associated with wide split of second heart sound due to delayed pulmonic closure and MR is associated with wide split of second heart sound due to early aortic closure.*

**39. Answer is D (LBBB):** *Hurst 12th /268; 'Cardiology' 3rd/6; Cleveland Clinic cardiology Board Rinen by Topol (2006)/33*

*LBBB is associated with reversed or paradoxical spitting of S2 and not with fixed splitting.*

Fixed splitting

Fixed splitting of $S_2$ is said to be present when the split does not vary with respiration and is present in both inspiration and expiration
This occurs due to minimum change in volume of right heart during inspiration and expiration

| Causes of Fixed (wide) split |
|---|
| • ***ASD (Most characteristic cause for wide fixed splitting)*** |
| • Pulmonic Stenosis |
| • *Acute Right Heart Failure (Pulmonary Embolism)* |

**40. Answer is B and C (WPW type A and LV pacing):** *Hurst 12th/268 (Refer table in earlier question)*

*WPW syndrome type A and LV pacing are not associated with reversed splitting. Reversed splitting from early pulmonic closure may be seen in WPW syndrome type B (Not type A) and RV pacing (Not LV Pacing)*

*LBBB, Hypertensive heart disease (Hypertension) and post–stenotic dilatation in AS are all associated with reversed splitting due to associated delayed Aortic closure.*

**Reversed Splitting of the second Heart Sound**

| Delayed aortic closure | Early pulmonic closure |
|---|---|
| • ***Right ventricular paced beat*** | *Early electrical activation of the right ventricle* |
| • ***Complete LBBB (peripheral type)*** | ***Wolff-Parkinson-White syndrome, type B*** |
| • ***Hypertensive cardiovascular disease*** | |

**41. Answer is A, C, E (TOF, Pulmonary Atresia, Severe Pulmonic stenosis):** *Hurst 12th/269; Sapira's Art and Science of Bedside diagnosis 3rd/350*

*TOF, Pulmonary Atresia and severe pulmonic stenosis are associated with single $S_2$ as one component of S2 is either absent or inaudible in these conditions.*

**Causes of single $S_2$**

| Conditions causing Delayed Aortic Closure | Conditions in which one component of $S_2$ is either absent or inaudible | Condition resulting in inability to hear the fainter of the two components of the sound (usually $P_2$) |
|---|---|---|
| All conditions associated with delayed $A_2$ can produce a single $S_2$ when the splitting interval becomes less than 30ms | Conditions in which one component of $S_2$ is either absent or in audible will produce a single $S_2$<br>• ***Severe TOF***<br>• Severe semilunor valve stenosis<br>- severe AS<br>- ***severe PS***<br>• ***Pulmonic valve atresia***<br>• Tricuspid valve atresia<br>• Eisseminger syndrome | These conditions also produce a single $S_2$<br>• Emphysema<br>• Obesity<br>• Respiratory noise |
| Causes of Delayed A2 *(Refer Table on abnormal splitting of S2)* | Semilunar valves include Aortic valve, Pulmonary valve and trancal valves | |

**42. Answer is A and C (Pulmonary hypertension and Eisenmenger's syndrome):** *Essential cardiology 2nd/108 Sapira's Art and science of Bed side diagnosis 3rd 1350*

*Loud $P_2$ suggests the presence of pulmonary Arterial Hypertension.*
*Eisenmerger's syndrome is associated with pulmonary arterial hypertension and hence also causes a loud $P_2$.*

Loud Pulmonary component of second Heart sound (Loud $P_2$)

- Loud Pulmonary component (P2) of the second heart sound signifies pulmonary arterial hypertension
  *'Unless proved otherwise a loud P2 is considered to be caused by Pulmonary Hypertension' - 'Understanding Pediatric Heart sounds (2002)/97*
- When a loud $P_2$ is described in the question, the most likely diagnosis is some form of pulmonary hypertension. Any etiological conditon leading to pulmonary hypertension may lead to a loud P2, including primary pulmonary hypertension, conditions of left side of heart (mitral stenosis), Eisenmenger's syndrome, or multiple pulmonary emboli.
- Eissenmenger's syndrome with Left to Right shunts leads to hyperkinetic pulmonary artery hypertension and may cause a loud P2

| Eisemenger's syndrome (Left to Right shunt): Loud P2 |
|---|
| ASD |
| VSD |
| PDA |

**Excluding other options**

- TOF : Loud A2
- Pulmonic Stenosis : Soft P2
- Aortic Stenosis : Soft A2

Note:

- A loud $P_2$ is predictive of significant pulmonary hypertension
- *$P_2$ may appear louder than $A_2$ if the intensity of $A_2$ is decreased as in calcific or rheumatic aortic stenosis but this is not due to an abnormally increased intensity of $P_2$*

## Third Heart Sound

**43. Answer is B (Mitral stenosis):** Harrison 18th/p 1827 *Harrison 15th/ 1259, Harrison 16th/ 1308; Harrison 17th/ 1386*

***The left ventricular function is essentially normal in mitral stenosis and $S_3$ is not a presenting feature.***

**The third heart sound** *($S_3$) is a low pitched sound produced in the ventricle 0.14 to 0.16s after $A_2$, at the termination of rapid filling.*

**Third Heart Sound (S3)**

- *It is a low frequency sound* Q
- *It is a diastolic heart sound that occurs shortly after S2* Q
- *It occurs during rapid filling of the ventricles (termination of rapid filling)* Q
- *It is best heard at the apex in the left lateral position* Q
- *It is better heard with the bell of the stethoscope* Q

**Third Heart Sound ($S_3$): Ventricular Diastolic Gallop, Protodiastolic Gallop, and Pericardial Knock**

| Physiologic $S_3$ | Pathologic $S_3$ |
|---|---|
| • Children<br>• High cardiac output<br>- ***Atheletes*** Q<br>- *Fever* Q<br>- *Pregnancy* Q<br>- *Thyrotoxicosis* Q<br>- *AV fistulas* Q | • ***Ventricular dysfunction (LVF/RVF)*** – poor systolic function, increased end-diastolic and end-systolic volume, decreased ejection fraction, and high filling pressure.<br>- Idiopathic dilated cardiomyopathy<br>- *Ischemic heart disease*<br>- Valvular heart disease<br>- Congenital heart disease<br>- Systemic and pulmonary hypertension<br>• Excessively rapid early diastolic ventricular filling<br>- Hyperkinetic states<br>- Anemia<br>- Thyrotoxicosis<br>- Arteriovenous fistula<br>- Atrioventricular valve incompetence<br>- ***Left to right shunts (VSD, PDA and ASD)***<br>• Restrictive myocardial or pericardial disease<br>• ***Constrictive pericarditis (pericardial knock)***<br>• Restrictive cardiomyopathy<br>• Hypertrophic cardiomyopathy. |

***Pericardial knock is $S_3$*** *that occurs earlier (0.1 to 0.12 after $A_2$) and is higher pitched than normal. It often occurs in patients with constrictive pericarditis. Its presence depends upon the restrictive effect of the adherent pericardium, which halts diastolic filling abruptly. – Harrison*

**44. Answer is A (Occurs due to rapid filling of the ventricles during atrial systole ):** Harrison 18th/p 1827 *Hurst 12th/270,271;Harrison 17th/1386*

***Third heart sound occurs at the end of early rapid filling phase of the ventricle but not at the time of atrial systole.***
*The heart sound associated with ventricular filling during atrial systole is the fourth heart sound (S4)*
*Fourth Heart sound occurs in association with an effective atrial contraction[Q] (It is presumably caused by in-rush of blood into the ventricles when the atria contracts and hence it is also called the 'Atrial Heart Sound')*

**Pathological Third Heart Sound (S3) may be associated with ASD and VSD**

*'A pathological S3 is often present in large left to right shunts due to high flow across the mitral valve with **VSD or patent ductus arteriosus** and with high flow across the tricuspid valve with **ASD**. The presence of this sound in these conditions does not imply congestive heart failure, and such patients may maintain normal myocardial contractility for years after the S3 is detected'- 'Hurst: The Heart' 11th/271*

| Congenital Heart Diseases associated with Loud S3 |
|---|
| • *Ventricular septal Defect (VSD)[Q]* |
| • *Patent Ductus Arteriosus (PDA)[Q]* |
| • *Atrial Septal Defect (ASD) [Q]* |

**Pathological Third Heart Sound (S3) may be associated with Constrictive Pericarditis**
Constrictive pericarditis is characterixstically associated with pericardial knock which is a distinct form of third heart sound ($S_3$)
***'Pericardial knock is $S_3$ that occurs earlier** (0.1 to 0.12 after A2) and is higher pitched than normal. Its presence depends upon the restrictive effects of the adherent pericardium which halts diastolic filling abruptly' – Harrison*

**45. Answer is C (Absent in MS):** Harrison 18th/p 1827 *Hurst 12th/272, Harrisons 17th/1386; Refer previous question*

*Third heart sound (S3) is commonly seen in association with ventricular dysfunction. Ventricular function is usually normal with MS and hence S3 is usually not a feature of MS.*

*Physiological S3 may be heard in athletes, while constrictive Pericarditis and ischaemic heart disease (MI) are established causes of pathological S3.*

## Fourth Heart Sound

**46. Answer is C (Heard during ventricular filling):** *Harrisons 16th/1308; Guyton 11th/270*

*The fourth heart sound (S4) is a low pitched presystolic sound produced in ventricles during ventricular filling – Harrison*

**Fourth Heart Sound (S4)**

- Fourth Heart sound occurs in association with an *effective atrial contraction[Q]*
  *(It is presumably caused by inrush of blood into the ventricles when the atria contracts and hence it is also called the 'Atrial Heart Sound')*
- ***It is heard during the ventricular filling phase of the cardiac cycle (Presystolic[Q] heart sound)***
- ***It is low pitched (frequency usually 20 cycle/sec or less-**(Guyton)*
- ***It is not audible to the unaided ear***

  Normally the fourth heart sound can almost never be heard even with a stethascope because of its weakness and low frequency *(Guyton)*
- S4 becomes audible when diminished ventricular compliance increases the resistance to normal filling
  When audible the S4 is *best heard with the bell of the stethescope[Q]*
- Pathologically may be seen in patients with
  - Systemic Hypertension
  - Aortic Stenosis
  - HOCM
  - Ischaemic Heart Disease
  - Mitral Regurgitation
  - Pulmonic stenosis (Right S4)
  - Pulmonary H.T (Right S4)

- Physiologically may be seen in patients with
  Increasing age
- Loudest (Best heard) at the Left ventricular Apex when the patient is in left Lateral position
- It is accentuated by mild isotonic or isometric exercises in the supine position

**47. Answer is C (Atrial Fibrillation):** Harrison 18th/p 1827 *Hurtz 12th/281; Harrisons 17th/ 1386*

*Atrial contraction must be present for production of S4. It is absent in atrial fibrillation.*
*Thyrotoxicosis. Acute MI, and Hypertrophic cardiomyopathy are all associated with pathological fourth Heart sound (S4).*

Fourth Heart Sound (S4):

- *Low frequency sound (low pitched)* Q
- *It is a diastolic heart sound that occurs shortly before S1* Q
- *It occurs during the phase of ventricular filling and is associated with an effective atrial contraction*
  *Atrial contraction must be present for production of an S4* Q
- *It is best heard at the apex in the left lateral position* Q
- *It is better heard with the bell of the stethescope* Q

Causes of Pathological Fourth Heart sound

**Fourth Hearth Sound (S4), Atrial Diastolic gallop, and Presystolic Gallop:**

**Decreased ventricular compliance**

- Ventricular hypertrophy
  - Left or right ventricular outflow obstruction
  - Systemic or pulmonary hypertension
  - Hypertrophic cardiomyopathy
- Ischemic heart disease
  - Angina pectoris
  - Acute myocardial infarction
  - Old myocardial infarction
  - Ventricular aneurysm
- Idiopathic dilated cardiomyopathy

**Excessively rapid late diastolic filling secondary to:**

- Vigorous atrial systole
- Hyperkinetic states
  - Anemia
  - Thyrotoxicosis
- Arteriovenous fistula
- Acute atrioventricular valve incompetence

**Arrhythmias**

- Heart block

***Physiologic S4 may be recordable, but is rarely audible***

**48. Answer is A (Ventricular aneurysm):** Harrison 18th/p 1827 *Harrison 15th/ 1259, Harrison 16th/ 1386; Harrison 17th/ 1386*

*In ventricular aneurysm the ventricle becomes more compliant than normal and offers lesser resistance to filling and hence no $S_4$ is heard. $S_4$ is characteristically absent in ventricular aneurysm due to increased ventricular compliance.*

**Fourth heart sound ($S_4$) :**

- Is low pitched, presystolic sound, produced in ventricle during *2nd rapid filling phase.*
- It is associated with *effective atrial contraction.*
- It occurs when there is increased resistance to ventricular filling due to *diminished ventricular compliance*

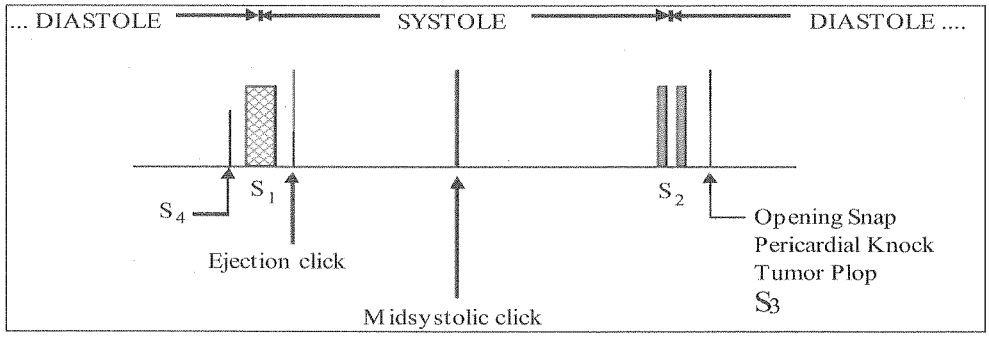
| Common conditions producing $S_4$ : | $S_4$ is absent in following conditions : |
|---|---|
| - ***Hypertension*** [Q]<br>- *Aortic stenosis* [Q]<br>- ***Hypertrophic cardiomyopathy*** [Q]<br>- *Ischaemic heart disease* [Q]<br>- ***Acute mitral regurgitation*** [Q] | - *Atrial fibrillation*<br>- *Ventricular aneurysm* |

## Added Sound

**49. Answer is C (Ejection click):** Harrison 18th/p 1826, 1827 *Harrison 14th/ 1234, 1235, 1341, 1339, Harrison 16th/ 1308; Harrison 17th/ 1385, 1386*

***Ejection click is a sharp high pitched sound*** [Q] ***that occurs immediately after First Heart Sound and not after the second.*** It occurs as a result of sudden opening of semilunar valves in conditions where this opening is delayed such as *Aortic valve stenosis* [Q], *Pulmonary valve stenosis* [Q], *Hypertension* [Q].

| Shortly after S1 [Q] | Shortly before S1 [Q] | Between S1 & S2 [Q] | Shortly after S2 [Q] |
|---|---|---|---|
| *Ejection click* | *Fourth heart sound* | *Midsystolic click* | *Opening snap / pericardial knock tumor plop / S3* |




| Ejection Click | Opening Snap | Pericardial knock | Tumor Plop |
|---|---|---|---|
| • *Sharp, High pitched sound* [Q] | • Brief, *High pitched sound* [Q] | • A third heart sound that is *higher pitched than normal* (S3 is low pitched). | • Tumor plop is a characteristic *low pitched sound* [Q] |
| • Audible during *early systole* [Q] *(immediately after S1)* | • Audible during *early diastole* [Q] *(between 0.04 to 0.12 sec after A2)* | • Audible during *early diastole* [Q] *(within 0.01 to 0.12 sec after A2)* | • Audible during *early or mid diastole* [Q] |
| • *Seen in Aortic stenosis* [Q], *Pulmonary stenosis* [Q], *Hypertension* [Q] *and is produced due to sudden opening of semilunar valves in conditions where this opening is delayed.* | • *Seen in stenosis of AV valves (Mitral stenosis* [Q] > Tricuspid stenosis) | • Seen in *constrictive pericarditis* [Q] and produced due to sudden deceleration of venticular filling because of restrictive effect of adherent pericardium. | • Seen in conditions like *atrial myxoma* [Q] and produced due to the tumor abruptly stopping as it strikes the ventricular wall |

**50. Answer is A (It is a high pitched diastolic sound):** Harrison 18th/p 1930 *Harrison 15th/ 1259, Harrison 16th/ 1308, 1311; 17th/ 1466, 1467*

***Opening snap is brief high pitched sound heard in early diastole.***

| *Opening snap* |
|---|
| - ***brief high pitched sound*** |
| - *heard in early* ***diastole*** *(Ejection sound are heard in systole)* |
| - *It is usually due to* ***stenosis of an (A.V.)*** *most often mitral value.* |
| - *It* ***follows second heart sound,*** *$A_2$ by 0.05 to 0.12 sec.* |
| - *It is generally best heard at* ***lower left sternal border*** *and radiates well to the base of heart* |

- *It is best heard during expiration*
- *The time interval between $A_2$ and $O_s$ varies inversely with the severity of M.S.*
- *It is followed by low pitched rumbling diastolic murmur*

**Note:**

- O.S. may also be audible in tricuspid stenosis
- O.S. of tricuspid stenosis occurs later in diastole than the mitral O.S.

***Opening snap indicates that :***

- *M.S. is organic (and significant)* ✓
- *Valve cusps are pliable* ✓
- *High atroventricular pressure gradient is present* ✓
- *Severe, AR, MR, AF, SABE are absent.* ✓

**51. Answer is D (Ejection click):** *Harrison 18th/p 1827 Harrisons 17th /1385, 1386 Braunward 8th/136*

*Ejection clicks are systolic sounds and not distolic sounds.*
*S3, S4 and opening snap are all diastolic sounds.*

Added Heart Sounds

| Diastolic sounds | Systolic sounds |
|---|---|
| • *Opening snap* ✓ | • *Ejection sound/click* ✓ |
| • *Third Heart sound (S3)* ✓ | • *Non ejection click/mid systolic click* ✓ |
| • *Fourth Heart sound (S4)* ✓ | |
| • *Pericardial knock* ✓ | |
| • *Tumor plop (Atrial myxoma)* ✓ | |

**52. Answer is A (MVP):** *Harrison 18th/ 1937 Harrison's 17th/1472; Refer Notes on 'MVP'*

*Midsystolic click is a characteristic feature of Mitral Valve Prolapse (MVP).*
*The prolapse of the mitral valve is the most common cause of Midsystolic clicks. Mitral Valve is typically associated with a midsystolic click and a late systolic ejection murmur*

**53. Answer is D (Pink TOF):** *Ghai 6th/385, 411; Moss & Adams Heart Disease in Infants, Children & Adolescents 7th/837; Pediatric Cardiology (2006) /59*

***Pink TOF (Acyanotic TOF) is unlikely to be associated with a Left upper parasternal systolic thrill.***

**Pink TOF is unlikely to be associated with a systolic thrill in 2nd & 3rd intercostal space**

Pink (Acyanotic) TOF is associated with only a mild degree of pulmonic stenosis.Such mild pulmonic stenosis is usually not associated with any thrill.

*"When pulmonic stenosis is mild the precordium is quiet and a thrill is not present"*
*- Moss & Adams Heart Disease in Infants, Children and Adolescents 7th/837*

*Thrill is usually associated with a moderate to severe degree of stenosis*
*When stenosis is mild a thrill is not present (Moss & Adams)*
*When stenosis is very severe (complete occlusion) thrill may be absent (Moss & Adams)*

*Systolic thrill in Left 2nd & 3rd intercostals space will be present when the associated pulmonic stenosis is at least a moderate degree. Such cases are usually associated with cyanotic TOF.*

**Systolic thrill in Left upper parasternal region is charachteristic of Pulmonic stenosis**

*'A systolic thrill in the second or third left intercostal space near the sternum often occurs with pulmonic stenosis'.*
*– Hurst 12th/256*

**Systolic thrill is Left parasternal region may be seen in Ebstein anomaly**

*'A systolic thrill may be palpable at the left sternal border' - Ghai 6th/411*

In Ebstein anomaly the septal leaflet of the tricuspid valve may be displaced into the RV outflow tract causing obstruction of antegrade flow into the pulmonary artery. ***This may produce a systolic thrill in the left parasternal region similar to Pulmonary stenosis (Upper Left parasternal area)***
*Also presence of tricuspid regurgitation in patients with Ebstein's anomaly may produce a systolic thrill at the left lower sternal border*

**Systolic thrill in Left upper parasternal region may be present in sub pulmonic VSD**

Subpulmonic VSD is a type of VSD where the defect is located in a more anterior portion in the ventricular septum such that *the VSD is closely related to the pulmonary artery.*
*In subpulmonic VSD the left ventricle 'Ejects' directly into the pulmonary artery which may in turn produce a systolic thrill in the pulmonary area (Left 2nd & 3rd intercostals space)*



## Cardiac Murmur

**54. Answer is D (Aortic stenosis):** Harrison 18th/p 1827, 1828 *Harrison 15th/ 207, 208; Harrison 16th/1309, 1310; Harrison 17th/ 1387*

**The murmur of Aortic Stenosis** *is characteristically an* ***ejection systolic murmur*** *Q that occurs in* ***midsystole*** *(starts only shortly after S1 and never with S1) when the ventricular pressure becomes high enough to open the semilunar valve. The murmur increases in intensity as the velocity of ejection increases and as ejection declines it decreases. The murmur ends before ventricular pressure falls enough to permit closure of aortic or pulmonary leaflets.*

**Systolic murmurs**

| Holosystolic /pan systolic murmurs | Midsystolic murmurs ejection systolic murmurs | | Early systolic murmurs |
|---|---|---|---|
| ***Begin with $S_1$ and end after $S_2$*** | ***Starts shortly after $S_1$ and ends before $S_2$*** | | ***Begin with first heart sound and end in midsystole*** |
| • VSD<br>• Mitral Regurgitation<br>• Tricuspid Regurgitation<br>• Aortopulmonary shunts | **Aortic** | **Pulmonary** | • VSD<br>- Large VSD with pulmonary hypertension<br>- *V. small muscular VSD*<br>• ***Tricuspid regurgitation*** in absence of Pul. Hypertension<br>• Mitral regurgitation in a non compliant left atrium as in ***papillary muscle dysfunction*** |
| | Aortic stenosis | P. stenosis | |
| | Coarctation | P. hypertension | |
| | Aneurysm | P. artery dilatation | |
| | PDA | ASD | |
| | High output states | High output states | |

**Common condition producing acute MR include**
- Rupture of chordae tendnae
- ***Papillary muscle dysfunction*** or rupture following MI
- Infective endocarditis

**55. Answer is D (Pansystolic murmur):** Harrison 18th/p 1944 *Harrisons 16th/ 1400; Harrison 17th/ 1476, 1475*

**Murmur in AR :** Harrison 16th/ 1400

| Typical **diastolic murmur** of chronic AR | **Midsystolic** ejection murmur | Austin flint murmur **(diastolic)** |
|---|---|---|
| • High pitched, blowing, decrescendo diastolic murmur<br>• Heard best in the third I.C.S. along the left sternal border<br>Note: With marked post stenotic dilatation of aorta the murmur may be loudest in the 2nd or 3rd right interspace – API 7th/ 420 | • Resembles murmur of AS but is higher pitched, shorter and less rasping<br>• Heard best at the base of heart and is transmitted along the carotids | • Soft, low pitched rumbling middiastolic<br>• Heard best at the apex<br>• Produced by diastolic displacement of anterior leaflet of mitral valve by AR stream |

**56. Answer is A (Mitral Stenosis):** *Harrison 17th /1467*

***Mid diastolic murmur with with presystolic accentuation is typically seen in mitral stenosis.***

*'Mitral stenosis is associated with a low-pitched rumbling diastolic murmur heard best at the apex. The murmur typically peaks during mid-diastole and again immediately before the first heart sound* ***(Pre-systolic accentuation)'***

*- Evidence Based physical diagnosis (Elsevier) 2012/397*

*'Mitral stenosis is associated with a low-pitched rumbling diastolic murmur heard best at the apex with the patient in lateral decubitus position. In patients with sinus rhythm, the murmur often reappears or becomes louder during atrial systole* ***(presystolic accentuation)'*** *- Harrison*

**Mitral stenosis : Review**

**Mitral stenosis**

**Auscultatory findings**

- **$S_1$ :** *accentuated.*
- **$S_2$ :** *Normally split $S_2$ with accentuated $P_2$*[Q]
- **Murmur :** *Low pitched*[Q]*, rumbling*[Q] *diastolic murmur*[Q] *with 'Pre-systolic accentuation' heard best at the apex in left lateral recumbent position*[Q]*.*
- **Opening snap** : *brief, high pitched*[Q]*, early diastolic*[Q] *sound, best heard at the lower left sternal border*[Q]*.*

**X Ray findings**

- *Straightening of the left border of cardiac silhouette*[Q]
- *Prominence of main pulmonary artery*[Q]
- *Dilation of upper lobe pulmonary veins*[Q]
- *Kerley B lines*[Q]
- *Backward displacement of the esophagus*[Q]

**57. Answer is D (HOCM):** *Harrison 18th/1830; Harrison's 17th/1387; Current Diagnosis & Treatment in Cardiology 2nd/144*

***Murmurs of HOCM are increased on Valsalva maneuver***
*Murmurs of VSD, MR and AS all decrease in intensity on Valsalva* ***maneuver***

**Differentiation of systolic murmurs base don changes in their intensity from physiologic maneuvers**

| Maneuver | HOCM | AS | MR/VSD | MVP | TR | Flow |
|---|---|---|---|---|---|---|
| Valsalva's maneuver | ↑ | ↓ | ↓ | ↑ | ↓ | ↓ |
| Stand | ↑ | - | - | ↑ | - | ↓ |
| Squat | ↓ | - | - | ↓ | - | ↑ |
| Handgrip/TAO | ↓ | - | ↑ | ↑ | - | ↓ |
| Inspiration | - | - | - | - | ↑ | - or ↑ |
| Post-PVC | ↑ | ↑ | - | - | - | ↑ |

AS= aortic stenosis; Flow = benign flow murmur; HOCM = hypertrophic obstructive cardiomyopathy; MR = mitral regurgitation; MVP = mitral valve prolapse; PVC = pressure ventricular contraction; TAO = transient arterial occlusion; TR = tricuspid regurgitation; VSD = ventriocular septal defect; ↑ = increased in murmur intensity; ↓ = decreased in murmur intensity; - = no predictable change

**58. Answer is C (MVP):** Harrison 18th/p 1830 *Harrison's 17th/1387; Current Diagnosis & Treatment in Cardiology 2nd/144*

***Murmur of MVP increases both on hand grip and on Valsalva maneuver. Murmur of HOCM increases on valsalva, but decreases on handgrip.***

| Maneuver | HOCM | MVP |
|---|---|---|
| Valsalva's maneuver | ↑ | ↑ |
| Handgrip/TAO | ↓ | ↑ |
| Stand | ↑ | ↑ |
| Squat | ↓ | ↓ |
| Inspiration | - | - |
| Post-PVC | ↑ | - |

**59. Answer is B (HOCM):** Harrison 18th/p 1830 *Harrison's 17th/1387; Braunwald 8th/ed 1663*

***Murmur of HOCM typically increases with Valsalva maneuver.***

*'Most murmurs decrease in length and intensity with Valsalva Maneuver. Two exceptions are the systolic murmur of HOCM which usually becomes much louder and that of MVP which becomes longer and often louder' – Harrison*

**60. Answer is C (Associated with AR) :** *Harrison 16th/1310; 17th/1387; API 8 th/438; CMDT 06/405; 09/365;Ghai 6th/376*

*Carey Coomb's murmur in a low pitched, delayed diastolic mitral murmur seen in rheumatic fever in association with Mitral Regurgitation. It is not associated with Aortic Regurgitation.*

| Carey Coomb's Murmur |
|---|
| • Low pitched (soft)<br>• Delayed diastolic (Middiastolic)<br>• Mitral<br>• Associated with Acute Rheumatic carditis<br><br>**Attributed to :**<br>• Inflammation of mitral valve cusps<br>• Excessive left atrial blood flow as consequence of mitral regurgitation |

| Austin Flint Murmur |
|---|
| • Low pitched (soft)<br>• Delayed diastolic (Middiastolic / Late diastolic)<br>• Mitral<br>• Associated with Aortic Regurgitation<br><br>**Attributed to :**<br>• Anterior mitral valve leaflet when blood enters the left ventricle simultaneously from both the aortic route and the left atrium |

*"Carey Coomb's murmur is a delayed diastolic mitral murmur." - Ghai 6th / 376*

**Remember :**
*Low pitched, delayed diastolic mitral murmur in association with Rheumatic fever : Carey Coomb's murmur.*
*Low pitched, delayed diastolic mitral murmur is association with severe chronic AR : Austin Flint murmur.*

**61. Answer is B (Acute Rheumatic carditis):** *Harrisons 17th/1387, Harrisons 16th/1310, API 8th/438,*

*Carey coombs murmur is delayed diastolic murmur seen in acute rheumatic carditis and is attributed to excessive left atrial blood flow due to mitral regurgitation.*
*It is not seen in MR, AR or severe pulmonary Hypertension.*

**62. Answer is A (AV Block):** ***Textbook of Cardiovascular Medicine by Topol 3rd/223***

*Rytand's murmur is a mid-diastolic murmur occasionally heard in patients with complete atrioventricular heart block (Complete A-V Block)*

**Rytand Murmur**

- Rytand's murmur is a mid-diastolic (or late-diastolic) murmur that is occasionally heard in patients with complete atrioventricular heart block,
- The mechanism of Rytand's murmur is not clear, but increased flow owing to slow heart rate and increased antegrade flow with atrial contraction, which occurs randomly, may be contributory.
- Rytand's murmur is best heard at the apex and may be confused with mitral stenosis.

*The slow heart rate, variable duration of the murmur, changing intensity of the S1, and lack of opening snap are helpful findings for the differential diagnosis*

**Named Diastolic Murmurs**

| *Named Diastolic Murmur* | *Condition* |
|---|---|
| *Carey Coombs murmur* | *Rheumatic fever* |
| *Austin Flint murmur* | *Aortic Regurgitation.* |
| *Graham- Steel murmur* | *Pulmonary regurgitation* |
| *Rytands murmur* | *Complete heart block.* |
| *Docks murmur* | *Left Anterior Descending (LAD) artery stenosis.* |

| **The 'water-wheel' or 'mill-wheel' murmur** |
|---|
| *The 'water-wheel' or 'mill-wheel' murmur is classically associated with large intracardiac air emboli and described as a "characteristic splashing auscultatory sound due to the presence of gas in the cardiac chambers.*<br>*May be heard due to air in RV cavity following cardiac catheterization.* |

**63. Answer is A (Mitral stenosis with Mitral Regurgitation ):** *Harrisons 17th/1388; Harrisons 16th/1311; Hurst's 12th/290*

*Continuous murmur is not associated with mitral stenosis and mitral regurgitation.*
*Patent ductus arteriosus, Rupture of sinus of valsalva and systemic AV fistutas are all associated with continuous murmurs.*

Causes of Continuous Murmur(Hurst)

| Continuous Murmur caused by Blood flow | Continuous murmurs caused by high-to low-pressure shunts | Continuous murmurs secondary to localized arterial obstruction |
|---|---|---|
| • Venous hum<br>• Mammary soufflé<br>• Hemangioma<br>• Hyperthyroidism<br>• Acute alcoholic hepatitis<br>• Hyperemia of neoplasm<br>- hepatoma<br>- renal cell carcinoma<br>- paget disease | Systemic artery to pulmonary artery<br>- Patient ductus arteriosus<br>- Aortopulmonary window<br>- Truncus arteriosus<br>- Pulmonary atresia<br>- Anamolous left coronary<br>- Bronchiectasis<br>- Sequestration of the lung<br>Systemic artery to right heart<br>- Ruptured sinus of Valsalva<br>- Coronary artery fistula<br>Left-to-right atrial shunting<br>- Lutembacher syndrome<br>- Mitral atresia plus atrial septal defect<br>Venovenous shunts<br>- Anomalous pulmonary veins<br>- Portosystemic shunts<br>Arteriovenous fistula (systemic or pulmonic) | • Coarctation of the aorta<br>• Branch pulmonary stenosis<br>• Carotid occlusion<br>• Celiac mesenteric occlusion<br>• Renal occlusion<br>• Femoral occlusion<br>• Coronary occlusion |

**64. Answer is D (Peripheral Pulmonary Stenosis):** Harrison 18th/p 1829 *Harrison 16th/ 1310, 1311; Harrison 17th/ 1386*

*The murmur of pulmonary stenosis is harsh systolic ejection murmur typically preceded by a systolic ejection sound. It is not a continuous murmur.*

**Continuous murmurs** result from continuous flow between a high pressure and low pressure area that persists through the end of systole and beginning of diastole.

**Common Causes of continuous murmurs**

- ***Systemic arteriovenous fistula*** ♀ (congenital /acquired)
- ***Coronary arteriovenous fistula*** ♀
- *Anomalous origin of Left coronary artery from pulmonary artery*
- ***Communication between sinus of valsalva and right side of heart*** ♀ ***(i.e. Ruptured sinus of valsalva*** ♀ ***into right side of heart)***
- ***Coarctation of Aorta : Continuous murmur in the back***
- ***Patent Ductus Arteriosus*** ♀ ***(PDA)***
- *Surgically created shunts e.g. Blalock-Tausig shunt*

**65. Answer is A (Ventricular septal defect with Aortic Regurgitation):** Harrison 18th/p 1829 *Harrisons 17th/1388; Refer previous question*

*Ventricular septal defect with Aortic Regurgitation does not produce a continuous murmur*

**Patent Ductus Arteriosus** produces a continuous murmur by the presence of a high to low pressure shunt
**Coronary AV fistula** also produces a continuous murmur by the presence of a high to low pressure shunt
**Venous hum** produces a continues murmur by rapid flow of blood
*Venous hum is a continues murmur usually audible over the medial aspect of the right supraclavicular fossa with the patient upright (Harrison)*

66. **Answer is A and C (PDA and Shunt between pulmonary & subclavian artery):** Harrison 18th/p 1829 *Hurzt 12th/290, Harrisons 17th/1388 Refer previous question*

*Shunts between systemic artery and pulmonary artery (includes PDA and shunt between pulmonary artery and subclavian artery) are associated with continuous murmurs.*

67. **Answer is B (Systemic A V fistula); D (Aortopulmonary window) and E (Rupture of sinus valsalva):** Harrison 18th/p 1829 *Harrisons 17th/1388: Hurst 12th/290*

*Aortopulmonary window, systemic AV fistula and ruptured sinus of valsalva are associated with continuous murmurs caused by high to low pressure shunting of blood.*

68. **Answer is A (Complete heart block):** Harrison 18th/p 1829 *CMDT 2008/323; CMDT 2009/321; 'Cardiology Secrets 2nd/113*

*Complete heart block is not a cause for new onset systolic murmur after Acute Myocardial Infarction.*

Cause of new systolic murmur after Acute Myocardial infarction

- *Papillary muscle dysfunction/rupture (causing severe mitral regurgitation)*
- *Rupture of interventricular septum*
- *Right ventricular infarction and tricuspid regurgitation*
- *Free wall rupture*
- *Left ventricular outflow tract obstruction*

Note:
***Ischemic cardiomyopathy*** *is defined as dilated cardiomyopathy in a subject with history of MI. This may lead to papillary muscle dysfunction and hence produce a new onset systolic murmur.*

## Cardiovascular Clubbing

69. **Answer is D (Aortic Dissection):** *Harrison 16th/211, 'Ultra Medicine' by Cockshoot and Monfredi (2005)/285*

**Aortic Dissection is not a known cause for digital clubbing:**
*Digital clubbing results from long standing conditions that take months to develop. It is not associated with acute event like aortic dissection*

Cardiovascular causes of Digital clubbing (Ultra medicine (2005)/285)

- *Subacute Bacterial Endocarditis(SBE)*
- *Cyanotic congenital Heart Disease*
  - *Tetralogy of Fallot (TOF)*
  - *Transposition of Great vessels (TGV)*
  - *Total Anomolous pulmonary venous circulation (TAPVC)*
  - *Ebstein's Anomaly*
  - ***Tricuspid Atresia***
- *Atrial Myxoma*
- *Arterio venous malformations (Brochial arteriovenous fistula)*
- *Axillary artery Aneurysms*

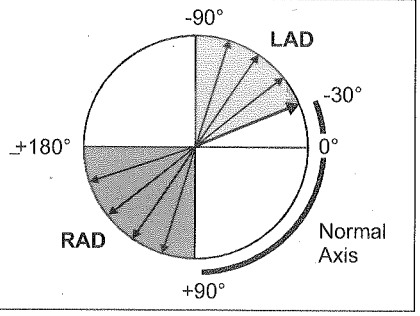
*Clubbing is a feature of Subacute Bacterial Endocarditis (SBE) and is not seen in Acute Bacterial Endocarditis Acute endocarditis is a fulminant event while clubbing takes months to develop. Acute bacterial endocarditis is not associated with clubbing.*

## Electrocardiogram and Arrhythmias

### Cardiac Axis

70. **Answer is A (-30 to +90):** *The EKG Handbook : Refer Review Notes on Cardiac Axis*

***The normal axis flows down and towards the left lower aspect of the heart between -30 to +90***

| Cardiac Axis | |
|---|---|
| Normal Cardiac Axis<br>Normal cardiac axis flows down and towards the left lower aspect of the heart between – 30 and +90<br>Left Axis Deviation<br>Cardiac axis flow is upward and towards the left upper half of the heart between -30 and -90<br>Right Axis Deviation<br>Cardiac axis flow is downwards and towards the right part of the heart between +90 and +/- 180<br>Extreme Right Axis Deviation<br>When flow of cardiac axis is upward and to the right between +/-180 and -90 |  |

**71. Answer is C (-30 to +90°):** *Refer Review Notes On Cardiac Axis*

*Normal cardiac axis flows down and towards the left lower aspect of the heart between – 30 and +90.*

**72. Answer is A (Left Axis Deviation):** *Refer Review Notes on Cardiac Axis*

*Deviation of the cardiac axis more negative than -30 (Between -30 to -90) indicates Left Axis Deviation.*

**73. Answer is A (Left Ventricle Hypertrophy):** *ECG Interpretation: From Pathophysiology to Clinical Application (Springer) 2009 /221; Electrocardiography for the Family Physician (Universal-Publishers) 2005/ 25, 26*

*Deviation of the cardiac axis more negative than -30 (Between -30 to -90) indicates Left Axis Deviation. Left Ventricular Hypertrophy is the most common cause of left axis deviation.*

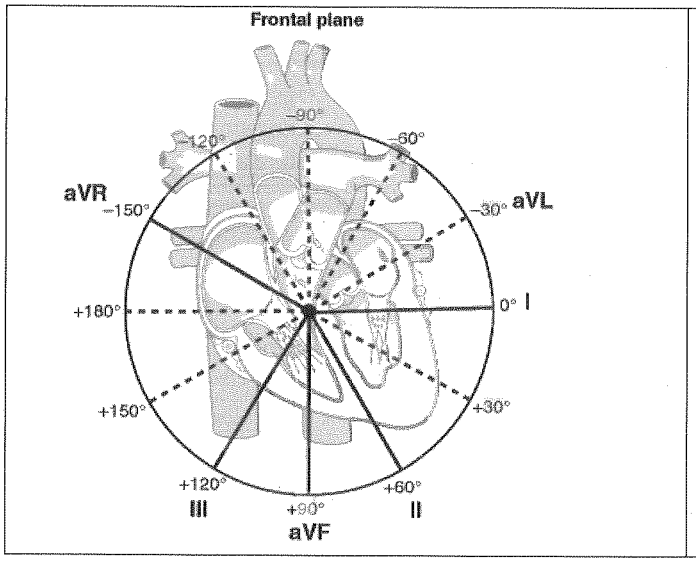
***Right Ventricle Hypertrophy, Left Posterior Fascicular Block and Lateral wall Myocardial Infarction are all associated with Right Axis Deviation.***

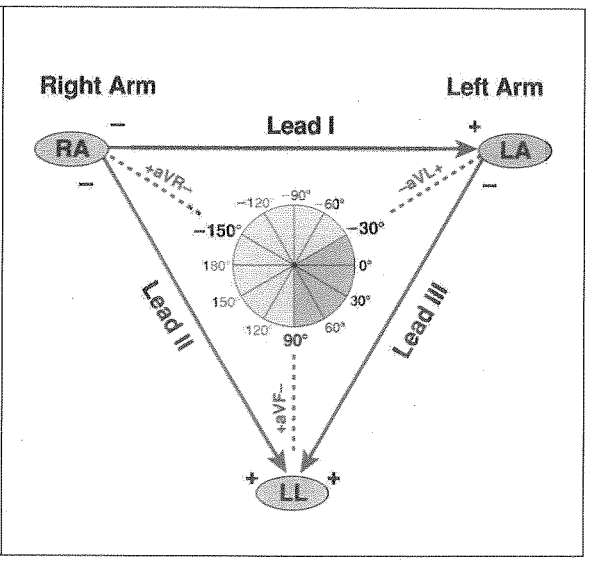
***Predominant Causes Of Axis Deviation***

| *Left Axis Deviation* | *Right Axis Deviation* |
|---|---|
| • *Left Anterior Fascicular Block* | • *Left Posterior Fascicular Block* |
| • *Left Ventricle Hypertrophy(All causes of LVH)* | • *Right Ventricle Hypertrophy(All causes of RVH)* |
| • *Inferior Wall Myocardial Infarction* | • *Lateral wall Myocardial Infarction* |

**74. Answer is B (Positive in Lead I and Negative in Lead II) :** *Harrison 17th /1764; Harrison's 18th/2312*

***Left axis deviation is seen as positive deflexion in Lead I and a Negative deflection in Lead II.***



Calculating the cardiac axis:

| | Normal Axis | Right axis deviation | Left axis deviation |
|---|---|---|---|
| Lead I | Positive | Negative | *Positive* |
| Lead II | Positive | Positive or negative | *Negative* |
| Lead III | Positive or negative | Positive | *Negative* |

| Note: |
|---|
| Lead I : POSITIVE BETWEEN -90 TO +90 (CLOCKWISE) |
| Lead II : POSITIVE BETWEEN -30 TO +150 (CLOCKWISE) |
| Lead III : POSITIVE BETWEEN +30 TO -150 (CLOCKWISE) |

## P wave

**75. Answer is A (Atrial Depolarization):** *Ganong 19th/526; Ganong 20th/532; Ganong 22nd/550, 551*

***P wave is produced due to atrial depolarization.***

| Intervals | Events in the Heart During Interval |
|---|---|
| P wave | *Atrial depolarization* |
| PR interval | *Atrial depolarization and conduction through AV node* |
| QRS duration | *Ventricular depolarization and atrial repolarization* |
| QT interval | *Ventricular depolarization plus ventricular repolarization* |
| ST interval (QT minus QRS) | *Ventricular repolarization* |

**76. Answer is D (aVR):** *Harrison 18th/1833*

***The normal P wave is negative (inverted) in lead aVR.***

***Characteristics of a Normal P Wave***

- P wave results from spread of electrical activity through the atria (Atrial Depolarization)
- A normal p wave indicates that the electrical impulse responsible for the p wave originated in the sinus node and the normal depolarization of the right and left atria has occurred
- Normal P Wave is rounded, neither peaked nor notched.
- Width or duration of the P wave in time is 0.10 seconds or 2.5 small squares
- Height of the P wave is 2.5 mm (2.5 small squares)
- *Sinus P waves are best seen in Lead II and V1*
- ***P wave is upright in most leads, mainly $L_I$ $L_{II}$ and aVF***
- ***P Wave is inverted in aVR*** (and occasionally in aVL)
- *P wave in $V_1$ may be biphasic* with equal upward and downward deflection, notched and wide. Activation of right atrium produces positive component and activation of left atrium produces negative component.
- There should be one p wave preceding each QRS complex. More than one p wave before a QRS complex indicates a conduction disturbance.

**77. Answer is A (V1):** *Harrison 18th/1833*

***Normal P wave may be seen as a Biphasic wave in lead V1.***

*'The normal P wave in lead V1 may be biphasic with a positive component reflecting right atrial depolarization followed by a small (<1mm$^2$) negative component reflecting left atrial depolarization' – Harrison*

*Note: The normal P wave is negative (inverted) in lead aVR.*

**78. Answer is A (Atrial Fibrillation):** *ECG Workout: Exercises in Arrhythmia Interpretation By Jane Huff (Lippincott Williams & Wilkins) 5th/ 16; ECG in Medical Practice By Abdullah(JP Medical)4th/ 14,15*

*P wave is typically absent in Atrial Fibrillation. COPD and Cor-Pulmonale are associated with tall p waves from Right Atrial Enlargement (P-Pulmonale) while Mitral Stenosis is typically associated with a wide and notched p wave from Left Atrial Enlargement (P-Mitrale)*

**Causes of Absent 'p' Wave:**

- *Atrial fibrillation ('p' wave is absent or replaced by fibrillary 'f' wave)*
- *Atrial flutter ('p' wave is replaced by flutter wave, which shows saw-tooth appearance).*
- *SA block or sinus arrest*
- *Nodal rhythm (usually abnormal, small p wave).*
- *Ventricular ectopic and ventricular tachycardia.*
- *Supraventricular tachycardia ('p' wave is hidden within QRS, due to tachycardia).*
- *Hyperkalemia.*
- *Idioventricular rhythm*

| | |
|---|---|
| *Right Atrial Enlargement(RAE) is typically associated with tall P waves (COPD and Cor-Pulmonale are associated with tall p waves from RAE)* | *P Pulmonale* |
| *Left Atrial enlargement(LAE) is typically associated with wide P waves (Mitral Stenosis is typically associated with a wide and notched p wave from LAE* | *P Mitrale* |

**79. Answer is C (Atrial Flutter with Fixed Block):** *Oxford Handbook of Acute Medicine(2010) /78*

*The absence of any discernible P waves on ECG, together with the presence of Saw Tooth Flutter waves in inferior leads (Leads II, III and AVF) strongly suggests a diagnosis of Atrial Flutter. The presence of a regular rhythm suggests a Fixed Block*

| Findings/Features | Diagnosis |
|---|---|
| Irregular Rhythm with no discernible P wave (Chaotic base line with fibrillary f waves) | Atrial Fibrillation |
| ***Irregular rhythm with no discernible P wave*** (*Saw tooth flutter* waves especially in inferior leads and V1) | *Atrial Flutter with variable block* |
| ***Regular rhythm with no discernible P waves*** (*Saw tooth flutter* waves especially in inferior leads and V1) | *Atrial Flutter with fixed block* |
| Irregular Rhythm with multiple P wave morphologies (P waves Discernible) and Varying PR intervals | Multifocal Atrial Tachycardia |

**80. Answer is A (Mitral Stenosis):** *ECG Workout: Exercises in Arrhythmia Interpretation by Jane Huff (Lippincott Williams & Wilkins) 5th/ 16; ECG in Medical Practice by Abdullah (JP Medical)4th/ 14,15*

*Mitral Stenosis is typically associated with a Wide and Notched P wave from Left Atrial Enlargement (LAE)*
***Cor-Pulmonale, COPD and Pulmonary embolism are all associated with Right Atrial Enlargement resulting in a Tall P wave (not a wide p wave)***

**P Wave in Right Atrial Enlargement (RAE)**

- Enlargement of the right atrium produces an abnormally ***Tall, Peaked P wave.***
- The abnormal p wave in right atrial enlargement (RAE) is sometimes referred to as ***'p-pulmonale'***
- The atrial enlargement that it signifies may be seen with *severe pulmonary disease (for example, chronic obstructive pulmonary disease, status asthmaticus, acute pulmonary embolism, and acute pulmonary edema). It is also common with congenital heart disease.*

**P Wave in Left Atrial Enlargement (LAE)**

- Enlargement of the left atrium produces a ***Wide and Notched P wave***
- The abnormal p wave seen in left atrial enlargement (LAE) is sometimes referred to as ***'p-mitrale'*** because they were first described in patients with rheumatic mitral valve disease.
- The atrial enlargement that it signifies may be seen with *mitral and aortic valvular disease, hypertension coronary artery disease, and cardiomyopathies*

Tall p is called p pulmonale
Height>2.5 mm, i.e.>2.5 small squares
*It is due to right atrial hypertrophy*

Broad and notched p is called p mitrale
Duration > 0.11 sec, or > 2.5 small squares
*It is due to left atrial hypertrophy*

## QRS Complex

**81. Answer is D (Ventricular depolarisation):** *Ganong 19th/526; Ganong 20th/532*

*QRS complex is due to ventricular depolarization* [9]

**82. Answer is D (Left Bundle Branch Block):** *Cleveland Clinic Cardiology Board Review (Lippincott Williams) Harrison's 18th/1835*

***Left Bundle Branch block is typically associated with a QRS duration greater than 120 milli seconds.***

*Partial Blocks (Fascicular or hemiblocks) in the left bundle system (left anterior or posterior fascicular blocks) generally do not prolong the QRS duration substantially and QRS duration typically remains less than 120 milliseconds.*

**QRS Complex Duration**

| < 0.10 sec (< 100 m sec) | Between 0.10 to 0.12 sec (Between 100 and 120 msec) | > 0.12 sec (>120 m sec) |
|---|---|---|
| *Normal* | **Inspect for features of:**<br>1. *Incomplete RBBB*<br>2. *Left Anterior Fascicular Block*<br>3. *Left Posterior Fascicular Block* | **Inspect for features of:**<br>1. *Right Bundle Branch block*<br>2. *Left Bundle Branch block*<br>3. *Intraventricular conduction delay (Hyperkalemia/Antiarrhythmics)* |
| | *May be normal* | |

Any QRS complex Duration > 0.12 seconds is abnormal. There are no exceptions to this rule
(A QRS complex Duration < 0.12 seconds may be normal)

**83. Answer is D (Left Anterior Fascicular Block):** *Harrison 18th /1835; '12 Lead ECG by Holtz (Jones and Barlett) 2011/QRS Duration*

***Left Anterior Fascicular Block is a partial block in the left bundle system and does not prolong the QRS duration significantly. Typically the QRS duration is slightly prolonged and remains between 0.10 to 0.12 seconds.***

**Causes of QRS Widening ≥ 0.12 seconds (in decreasing order of mortality)**

- ***Hyperkalemia***
- ***Ventricular Tachycardia (Wide complex Tachycardia)***
- *Idioventricular Rhythm including heart blocks*

  *Wide QRS complex may be seen in Mobitz Type II second degree block and incomplete Third Degree Blocks but lacks certainity*

- *Drug effects and overdoses (especially Tricyclics)*
- ***Wolf Parkinson White syndrome***
- *LBBB; RBBB; Intraventricular conduction delay*
- *Ventricular premature contraction*
- *Aberrantly conducted complexes*

**84. Answer is A (Bundle Branch blocks):** *Harrison 18th /1835; 'ECG Interpretation: From Pathophysiology to clinical Application' by Kusmoto (Springer) 2009/219*

***A wide QRS interval (Wide QRS complex) is most commonly caused due to abnormal conduction over the left or right blundle due to block or delay of ventricular activation (Bundle branch blocks).***

*Wide QRS complex may also be seen in mobitz type II block, but lacks certainity*

**QRS complex: Wide or Narrow**

- QRS complex represents ventricular depolarization and QRS interval represents the duration of ventricular depolarization.

The normal QRS interval (QRS duration) is less than 0.10 to 0.11 seconds.

- If the QRS complex is less than 0.12 second, ventricular depolarization is more or less occurring normally over the His-Purkinje system.
- There are several causes for a wide QRS complex, which result from abnormal activation of the ventricles.
- ***Most commonly, a wide QRS complex is due to abnormal conduction over the right or left bundle due to block or delay of ventricular activation.***
- Rarely, a wide QRS complex is observed because the ventricles are being activated via both the His-Purkinje system and an accessory pathway.
- With greater use of cardiac devices, a wide QRS complex will be observed in patients with pacemakers where the ventricle is being activated artificially from an electrical impulse delivered via a ventricular pacing lead.

Wide QRS complex with a nomtal rate: abnormal ventricular activation

| Condition | Pathophysiology | ECG findings |
|---|---|---|
| ***Bundle branch block*** | *Block in the right or left bundle leads to sequential activation of the right and left ventricles* | In right bundle branch block an rSR' will be seen in lead $V_1$ and in left bundle branch block a wide predominantly negative QRS complex will be seen |
| ***Accessory pathway*** | *The ventricles are activated by both the AV node and an accessory pathway* | The PR interval will be short due to early ventricular activation from the accessory pathway and the QRScomplex will be abnormal because of cell-to-cell activation of ventricular tissue |
| ***Hyperkalemia*** | *High levels of potassium lead to slow ventricular depolarization* | Prominent T waves will often be observed |
| ***Ventricular rhythm*** | *A site within the ventricles drives ventricular depolarization* | P waves will not precede the QRS complexes |
| ***Ventricular paced rhythm*** | *Similar to the ventricular rhythm* | A pacing artifact will be observed |

**85. Answer is D (Increased cardiac muscle mass):** *Ganong Review of Medical Physiology 22nd/550; Guyton 10th/127*

*The normal voltage in the three standard leads as measured from the peak of R wave to the bottom of S wave is 0.5 – 2.0 millivolts.* When the sum of *voltages of all the QRS complexes of the three standard leads is greater than 4 millivolts*, the ECG is considered **as *high voltage electrocardiogram*. Most often this is due to *increased cardiac muscle mass*[Q].**

**86. Answer is B (Pericardial effusion):** *'ECG Interpretation: From Pathophysiology to Clinical Interpretation (Springer) 2009/281; '150 Practice ECGs Interpretation & Review' by Taylor (John Wiley & Sons) 2003/48, 49*

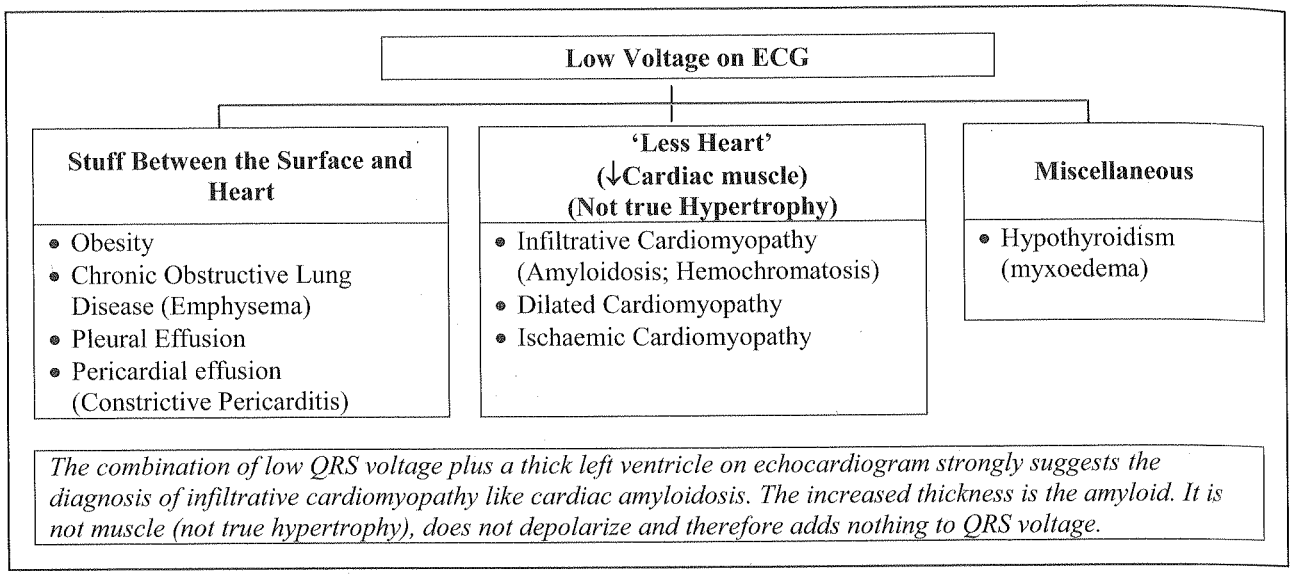
***Cardiac conditions associated with low QRS voltage on ECG include dilated cardiomyopathy, infiltrative cardiomyopathy, pericardial effusion and constrictive pericarditis' - 150 Practice ECG's***

Low QRS voltage on ECG

- Diagnostic criteria for Low QRS voltage include QRS complex amplitude < 5mm in all limb leads (*when this is the case the amplitude in each of the precordial leads (V) is usually less than 10 mm, but this is not necessary for the diagnosis)*

| Low QRS voltage or ECG |
|---|
| • *QRS amplitude <5 mm on all limb leads* |
| • *QRS amplitude < 10 mm on all precordial leads* |

- Low QRS voltage should be considered a description and not a diagnosis (it may be a normal variant)






**87. Answer is B (Cardiac Amyloidosis):** *'150 Practice ECGs Interpretation and Review' by Taylor (John Wiley & Sons 2008/49)*

***Low QRS voltage on ECG with left ventricular hypertrophy on Echocardiography suggests a diagnosis of infiltrative cardiomyopathy like amyloidosis.***

*The combination of low QRS voltage plus a thick left ventricle on echocardiogram strongly suggests the diagnosis of infiltrative cardiomyopathy like cardiac amyloidosis. The increased thickness is the amyloid. It is not muscle (not true hypertrophy), does not depolarize and therefore adds nothing to QRS voltage.*

**88. Answer is C (35):** *Evidence-Based Medicine Guidelines / 99; Multiple Lead ECGs: A Practical Analysis of Arrhythmias By Kathryn Lewis / 219*

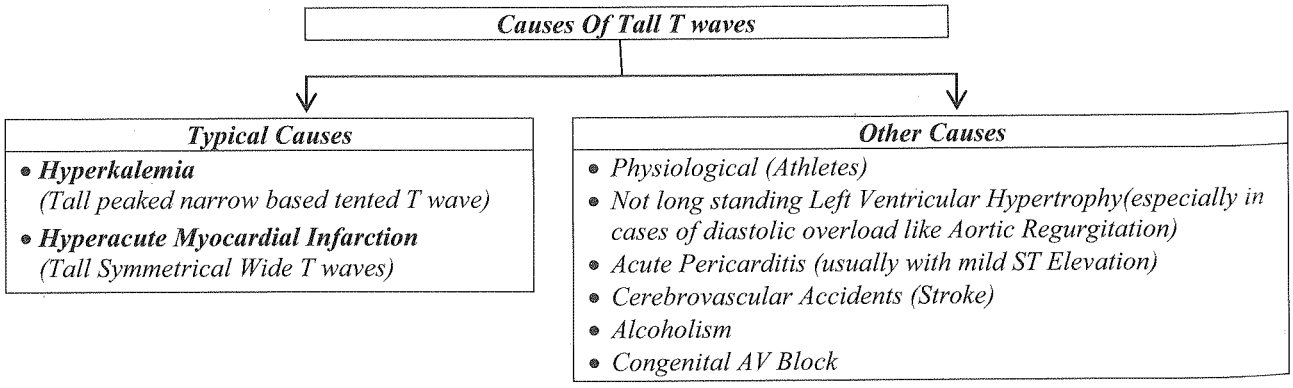
*In LVH, SV-1 plus RV-6 is more than 35 mm.*

| **Sokolow-Lyon and R/S Voltage Criteria for Left Ventricular Hypertrophy** |
|---|
| ▪ Look at leads $V_1$, $V_5$, and $V_6$. |
| ▪ When the S wave in $V_1$ plus the R wave in $V_5$ or $V_6$ is 35mm or greater, it is positive for LVH $SV_1 + RV_5$ or $RV_6 = \geq 35$ mm indicates LVH. |

## T wave

**89. Answer is A (Hyperkalemia):** *API Textbook of Medicine/ 575; Clinical Examination In Cardiology by Rao/495,496;*

*Hyperkalemia is typically associated with Tall peaked narrow based tented T wave.*



## ST Segment

**90. Answer is C (Constrictive pericarditis):** *Harrison 15th/ 1371; Harrison 16th/1317; 17th/ 1394, 1395; Other texts*

*ST segment elevation is seen in Acute pericarditis not constrictive pericarditis. Constrictive pericarditis is associated with flattening or inversion of T waves.*

**ECG findings of constrictive pericarditis include :**

- *Low voltage QRS complexes in all leads*
- *Diffuse flattening or inversion of T waves.*

**ST segment** is measured from the end of QRS complex to the beginning of the T wave, and represents the time interval between ventricular depolarization and repolarization.

**Abnormalities in ST segment are:**

| *Elevated* Q | | *Depressed* Q | | |
|---|---|---|---|---|
| With convexity upwards | With concavity upwards | Oblique Plane or Sagging | With mirror image of a correction mark | With convexity upwards |
| ↓ | ↓ | ↓ | ↓ | ↓ |
| Acute MI Q<br>LV aneurysm Q<br>Prinzemetal angina Q | Acute pericarditis Q | Coronary artery disease Q<br>(Angina pectoris) | Digitalis Q | In strain pattern of ventricular hypertrophy |

**91. Answer is B (Constrictive pericarditis) :** Harrison 18th/p 1837, 1838 *Harrison 16th/1318; Harrison 17th/ 1395; Previous question*

*ST segment elevation is seen in acute pericarditis and not in constrictive pericarditis*

**Causes of ST segment elevation**

| Common causes | Rare causes |
|---|---|
| • Acute myocardial infarction | • Brugada syndrome |
| • Prinzemetal angina (Non infarction transmural ischaemia) | • Class I C antiarrhythmic drugs |
| • Ventricular aneurysm (Post myocardial infarction) | • DC cardioversion |
| • Acute pericarditis | • Hyperkalemia |
| • ***Normal variant ('early repolarization' pattern)*** | • Hypothermia (J wave / Osborn wave) |
| • L.V. hypertrophy/ left bundle branch block | • Myocardial injury (Myocarditis Trauma, Tumor invasion) |

*Brugada syndrome shows RBBB like pattern with ST elevation) in right precordial leads**

**92. Answer is C (ST segment elevation):** Harrison 18th/p 1395 *Harrison 16th/ 1317; 17th/ 1393; Oxford handbook of clinical medicine 5th/88.*

**E.C.G. changes in acute infarction**

| **Early acute phase** *(within hours)* | **Fully evolved phase** | **Old infarction** *(resolution phase)* |
|---|---|---|
| • *Elevation of ST segment* | • *Pathological Q wave* | • *Pathological Q wave* |
| • *Tall wide (peaked) T wave* | • *Elevated ST segment beings to resolve* | • *ST segment and T wave may be normal* |
| | • *T wave inverts* | |

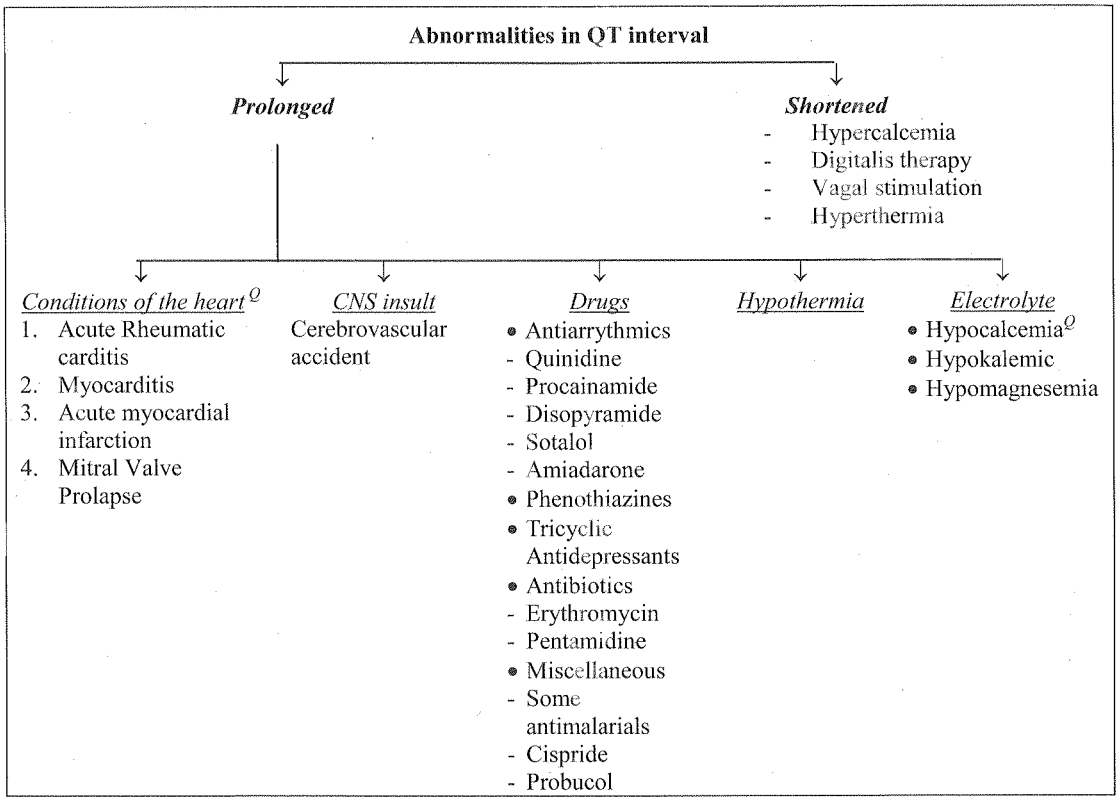
## QT Interval

**93. Answer is B (Digitalis toxity):** Harrison 18th/p 1836 *Harrison 16th/ 1319; Harrison 17th/ 1395; Kundu II/ 89; Braunwald 8th/906*

*QT interval is shortened in digitalis toxity and not prolonged*

**QT interval**

- Is measured from the beginning of Q wave to the end of T wave Q
- It is the time taken for total ventricular events i.e. depolarization as well as repolarization Q
- Normal QT interval should not exceed 42 seconds






**94. Answer is C (Hypercalcemia):** Harrison 18th/p 1836 *Harrisons 17th/1395; Hurst 12th/312*

*Hypercalcemia Shortens the QT interval*

***Causes of Short QT interval***

***Hypercalcemia***
*Digitalis glycosides*
*Hyperthermia (Hurst)*
*Some causes of hyperkalemia (Hurst)*
*Altered Autonomic tone (vagal stimulation)*
*Congenital short QT Syndrome*

**95. Answer is B (Decreased QT interval):** Harrison 18th/p 1838 *Harrisons 17th/1395; Harrisons 16th/1318, 1319*

*Hypercalcemia is characterized by a decreased QT interval.*

**96. Answer is C (Shortening of QT interval on ECG):** Harrison 18th/p 1838 *Harrisons 17th/1395*

*The QT interval on ECG is prolonged in hypocalcemia and shortened in hypercalcemia.*

***Manifestations of chronic hypocalcemia***

| Neuromuscular and Neurological | Mental changes | Miscellaneous | Cardiovascular |
|---|---|---|---|
| *Muscle spasms Q*<br>*Carpopedal spasms Q*<br>*Facial grimacing Q*<br>*Laryngeal spasms Q*<br>*Convulsions Q*<br>*Circumoral tingling Q* | Irritability<br>Depression<br>Psychosis | Respiratory arrest<br>*Increased ICT with papilloedema Q*<br>Intestinal cramps<br>Chronic malabsorption | Arrythmias<br>*Prolonged QT interval Q*<br>*Reduced effectiveness of digitalis Q* |

Low serum calcium leads to increased excitability of peripheral nerves and hence ***hyperactive tendon reflexes*** is a distinctive finding.

***Chrostek's or Trausseau's sign*** can be used ***to confirm Latent tetany*** when signs of overt tetany are lacking

| **Chvostek's Sign**$^{Q}$ | **Trousseau's Sign**$^{Q}$ |
|---|---|
| Tapping over the branches of the facial nerve as they emerge from the parotid gland produces twitching of the facial muscles | Inflation of Sphygmomanometer cuff on the upper arm to more than systolic BP is followed by carpal spasm within 3 minutes |

## Hypo/Hyperkalemia

**97. Answer is D (QT Interval prolongation):** Harrison 18th/p 1838 *ECG made easy; Harrison 16th/ 1318; Harrison 17th/ 1395; other references*
*The cardiac patient: A comprehensive approach by Sanderson and Becker 1st (1972)/191; Pocket Guide to Diagnostic Tests by Nicolle, Mc Phee (Lange) 4th/330*

**ECG changes**

**Characteristic features of Hypokalemia**

- ***ST depression*** $^{Q}$
- ***Flattened or inverted T wave*** $^{Q}$
- ***Prominent U wave*** $^{Q}$
- Prolonged P-R interval $^{Q}$
- Prolonged QU interval (Real)
- Rarely S-A block

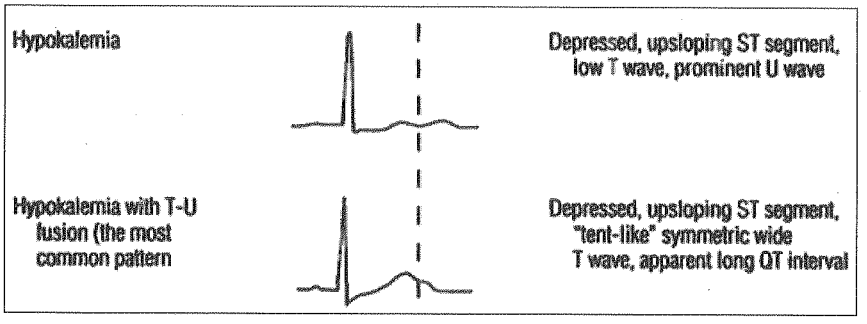
**Characteristic features of Hyperkalemia**

| | |
|---|---|
| Early | • Increased T wave amplitude $^{Q}$ Peaked T waves |
| Later (with severe degrees of hyperkalemia) | • Prolonged PR interval $^{Q}$<br>• Prolonged QRS duration $^{Q}$<br>• AV conduction delay<br>• Loss of P waves $^{Q}$<br>• Sine wave pattern $^{Q}$<br>• Ventricular fibrillation or asystole |

*Prominent U wave, ST segment sagging and T-wave flattening or inversion are characteristic features of Hypokalemia. Hypokalemia may also present with a apparently prolonged QT interval on ECG. However this apparently prolonged QT interval is in* reality the QU interval that mimics a prolonged QT interval due to fusion of T-U waves.
***Prolonged QT interval is the single best answer of exclusion.***

**QT interval and Hypokalemia**

- Hypokalemia causes an 'apparent' prolongation of the QT interval but the real QT interval remains 'normal'
- The apparent prolongation of QT interval is due to fusion of the T and U waves (T-U fusion)




- The prolonged QT interval that is 'apparent' in hypokalemia is actually (in reality) a QU interval.
- Wgere T and U waves are separate and distinct, the QT interval is normal but the QU interval is prolonged.

**98. Answer is A (Increased PR interval with ST depression):** *Repeat*

*Hypokalemia is associated with ST depression, prolonged PR interval, Flattened or Inverted T waves, Prominent U waves and rarely S - A block*

*Hypokalemia is associated with a prolonged QU interval and not a prolonged QT interval (Refer previous question)*

***Increased PR interval with ST depression therefore remains the single best answer of choice.***

***Note:***

- *QT interval is prolonged in Hypocalcemia* Q
- *QT interval is decreased in Hypercalcemia* Q

**99. Answer is B (Prolonged QT interval):** *Refer text below*

*Prolonged QT interval is a manifestation of hypocalcemia*

*An apparently prolonged QT interval may be associated with hypokalemia but is not a feature of hyperkalemia Prolonged PR interval, Sine wave pattern and loss of P waves may all be seen with hyperkalemia*

**ECG changes in hyperkalemia**

| | |
|---|---|
| Early | • *Increased T wave amplitude* Q *Peaked T waves* |
| Later (with severe degrees of hyperkalemia) | • *Prolonged PR interval* Q<br>• *Prolonged QRS duration* Q<br>• *AV conduction delay*<br>• *Loss of P waves* Q<br>• *Sine wave pattern* Q<br>• *Ventricular fibrillation or asystole* |

**100. Answer is C (Prolonged QT interval):** Harrison 18th/p 1838 *Harrison 16th /1318; Harrison 17th/ 1395;Refer previous question*

*Prolonged QT interval is not a manifestation of hyperkalemia. Prolonged PR interval, prolonged QRS duration and ventricular asystole are all known manifestations of hyperkalemia. Prolonged QT interval is a manifestation of Hypocalcemia.*

## Digitalis Toxicity

**101. Answer is C (Atrial flutter):** Harrison 18th/p 1897 *Harrison 16th/ 1375; Harrison 15th/1327; Harrison 17th/ 1441*

*"Digitalis is Profibrillatory but its administration does not cause Atrial Flutter"*

*Digitalis causes several disturbances in cardiac rhythm. Various manifestations seen are elaborated in the table below. Atrial Flutter has notably not been mentioned.*

| Manifestations of digitalis toxicity | |
|---|---|
| **Cardiac manifestations** | **Extracardiac manifestations** |
| *Disturbance in cardiac rhythm*<br>• *Ventricular premature beats*<br>• *Bigeminy*<br>• *Ventricular tachycardia*<br>• *Ventricular fibrillation*<br>• *A.V. Block of varying degree of severity may occur.* | • *Anorexia, nausea & vomiting (earliest sign)*<br>• *Weight loss*<br>• *Cachexia*<br>• *Neuralgias*Q<br>• *Gynaecomastia*Q<br>• *Yellow vision*Q<br>• *Delirium*Q |
| ***Non paroxysmal atrial tachycardia with variable A.V. Block is characteristic of Digitalis intoxication*** | |

***Also remember :*** *Mobile type II block is not seen in digitalis intoxication* Q

## Miscellaneous

**102. Answer is A (Left axis deviation):** *Diagnosis and treatment of diseases of the Respiratory tract by Iruvin Curley, Grossman (1997) / 236; Textbook of Cardiovascular medicine by Topol 3rd/988*

*Left sided penumotharax is associated with right axis deviation and not left axis deviation*

**ECG Changes in left sided Pneumothorax**

*ECG changed in pneumothorax, specially on the left, are important as there may mimic ECG, changes of acute MI*
**These include**
***Right ward deviation of QRS axis (Right axis deviation)***
*Decreased/absent R waves in the precordial leads*
*T wave inversion in precordial leads*
*Pathological Q waves*
*Decreased QRS voltage*
*Electrical alternans (alternating QRS amplitude with each heart beat)*

**103. Answer is B (Left axis deviation):** *See below*

*A left sided pneumothorax will shift the axis of the heart towards the right leading to a right axis deviation rather than a left axis deviation.*

## Arrhythmias

### AF and PSVT

**104. Answer is B (Hypothroidism):** Harrison 18th/p 1881 *Harrison 16th/1345; Harrisons 17th/1428; CMDT 2008/330; ; CMDT 2009/336; CEMDT (Emergency Medicine) 6th/582*

*Atrial Fibrillation is associated with hyperthyroidism and not hypothyroidism*

Important causes of Atrial Fibrillation

| Cardiovascular causes of Atrial Fibrillation | Other Systemic Causes of AF |
|---|---|
| • ***Rheumatic Heart disease (Includes mitral stenosis and mitral regurgitation)*** | • ***Hyperthroidism*** |
| • *Non Rheumatic Mitral valve disease* | • *Pulmonary embolism* |
| • *Chronic Hypertension* | • *Hypoxia* |
| • ***Cardiomyopathy*** | • *Excess consumption of alcohol (Also alcohol withdraw)* |
| • *Myocarditis* | • *Excess consumption of Caffeine* |
| • *Pericarditis* | • *May be seen in normal individuals* |
| • *Congenital Heart Disease (eg ASD)* | • *Particularly during emotional stress or following surgery, exercise or prominent surge of vagal tone (vasovagal response)* |
| • *Coronary Heart Disease* | |

*AF often develops in patients with heart or lung disease who develop hypoxia, hypercapria or metabolic or hemodynamic derangements*
*Holiday Heart Syndrome: In predisposed individuals, AF may be precipitated by consumption of even small amounts of alcohol. This is called Holiday Syndrome and is usually transient and self limited*

**105. Answer is B (Atrial Fibrillation):** *Harrison 18th/1880; Key Clinical Topics in Critical Care (JP) 2014/76*

*Atrial Fibrillation is the most common arrhythmia seen in the General Intensive Care Unit (ICU).*

**106. Answer is D (Atrial fibrillation):** Harrison 18th/p 1881 *Harrison 15th/1360; Harrison 16th/1409, 1410; Harrison 17th/1428*

*Atrial fibrillation is the most common arrhythmia appearing after a drinking binge. Fibrillation is followed by atrial flutter and ventricular premature depolarization in frequency.*

Alcoholic Cardiotoxity may present as

**Holiday heart syndrome**
- Typically appears after a drinking binge
- Presents with arrhythmias without overt heart failure
  - Atrial fibrillation is seen most frequently - *Harrison*
  - Atrial flutter
  - Ventricular premature depolarization

**Dilated cardiomyopathy**
- Seen with chronic consumption of large quantities of alcohol
- Presents with heart failure.

**107. Answer is C (Anticoagulation not required):** Harrison 18th/p 1882, 1883 *CMDT 2008/331; CMDT 2009/338; Harrisons 17th/1428, 1429*

***Anticoagulation is required in patients with Atrial fibrillation.***

**AF is associated with increased risk of Thromboembolism**

Atrial fibrillation is associated risk with increased risk of thromboembolism as a result of stasis of blood and thrombus formation in left atrium

AF is thus an important risk factor for stroke and systemic embolism

**Anticoagulation is required in patients with AF**

Because of increased risk of stroke in association with AF, anticoagulation is of particular importance in patients who have known risk factors for AF.

Urgent Anticoagulation is achieved with Heparin.

Chronic anticoagulation is achieved with Warfarin.

**Aspirin may be used as an alternative to Warfarin for some patients to achieve anticoagulation (Low risk patients)**

Anticoagulation

| Low risk | High risk |
|---|---|
| No therapy or Aspirin | Warfarin |

*Evidence for Aspirin prophylaxis is weaker than that for warfarin*

**Digoxin is required for treatment of AF**

Digoxin is indicated for control of ventricular rate in patient with AF.

**108. Answer is A (Digitalis toxicity) :** *Harrison 16th / 1345, 1375, 1394; CMDT 2008/347*

***The patient in question has a complete heart block most likely from digitalis intoxication.***

*'If in the presence of atrial fibrillation the ventricular rhythm becomes slow and regular (30 - 60 / m) complete heart block is suggested. Digitalis intoxication is a common cause.' - Harrison*

**Approach to Patient in question :**

- The patient in question is likely to be on digitalis for heart failure (due to MR) and to control ventricular rate from AF.
  *'Digitalis is effective in patients with heart failure complicated by atrial flutter and fibrillation and a rapid ventricular rate, who benefit both from slowing of the ventricular rate and from positive inotropic effect'. -Harrison*
- *The presence of a slow ventricular rate (30 - 60 / min) in presence of AF suggests complete AV block* and subsidiary ectopic pacemaker activity. *Syncope is likely to be a manifestation of complete heart block which in turn is a common complication of digitalis intoxication.*

**109. Answer is B (Digitalis toxicity):** *Harrison 15th/ 1295, Harrison 16th/ 1375*

*"If in the presence of atrial fibrillation, the ventricular rhythm becomes regular and slow (30 to 60/m) complete heart block is suggested and if ventricular rhythm is regular and rapid > = 100/ min, a tachycardia arising in AV junction or ventricle should be suspected. Digitalis intoxication is a common cause of both phenomenon" – Harrison*

**The patient in question has a regular ventricular rate despite fibrillating atria (irregularly beating atria)**

This indicates that

| | |
|---|---|
| All supraventricular impulses are blocked from reaching the ventricle somewhere within the conducting system.<br>- Complete A.V block | Ventricles are activated by a subsidery ectopic pacemaker situated either<br>- In the A.V node below the level of block<br>- Within the ventricles<br>(Such a subsidery pacemaker is usually slow and fires at the rate of 30-60/sec.) |

***Digitalis toxicity is a common cause of such a presentation and hence has been picked up as the answer of choice. Infact "Non paroxysmal atrial tachycardia with AV block is characteristic of digitalis intoxication."***

**110. Answer is D (Adenosine):** *Harrison 14th/ 1268; KDT 4th/ 516; Harrison 15th/ 1299; Harrison 16th/ 1347; 17th/ 1433*

*Drug of choice for PSVT is Adenosine*

| Agents of First choice include | Agent of second choice are |
|---|---|
| Adenosine (Drug of choice)<br>Verapamil | β *blockers* Q |

*Adenosine is preferred over Verapamil because of its extremely short half life, and lesser incidence of side effects* Q
*Thus DOC for PSVT is Adenosine.* Q

**111. Answer is C (Adenosine):** *Harrison 14th/ 1268; KDT 4th/ 516; Harrison 15th/ 1299; Harrison 16th/ 1347; 17th/ 1433*

*Drug of choice for PSVT is Adenosine.*

**112. Answer is A (Adenosine):** *Repeat*; *Harrison 17th/ 1433*

*Drug of choice to control supraventricular tachycardia is adenosine.*

**113. Answer is C (Verapamil)**: *Harrison 18th*

*Amongst the options provided Verapamil is the drug of choice for maintenance therapy in patients with PSVT.*

| Maintenance therapy in patients with PSVT |
|---|
| • Not required in all people.<br>• The frequency and severity of the episodes of SVT need to be balanced against the risks of long-term therapy.<br>• The choice of maintenance therapy depends on the underlying type of SVT<br>• Radiofrequency catheter ablation is recommended as the treatment of choice for most of these patients.<br>• Recommended drugs for Maintenance therapy or long term treatment include atrioventricular nodal blocking drugs (Calcium channel blockers-Verapamil, Beta blockers or digoxin) and antiarrhythmic drugs of Class Ic and Class III (Flecainide and sotalol)<br>• Beta blockers and calcium-channel blockers (Class II and IV) are suitable first-line treatments<br>• Randomised studies have not demonstrated clinical superiority of any single agent, but beta blockers and calcium-channel blockers are perceived to be superior to digoxin as they provide better atrioventricular nodal blocking action during states of high sympathetic tone, such as exercise<br>• Amiodarone has no role in long-term prevention of SVT, owing to the high incidence of serious toxicities associated with its long-term |

## VT, VF and PVCs

**114. Answer is B (Ventricular rate > 160/min):** Harrison 18th/p 1892, 1893 *Harrisons 16th/1351; Harrison 17th/ 1437; CMDT 2002/ 416; CMDT 2009/342; Oxford handbook of medicine 5th/110*

***In both ventricular and supraventricular tachycardia the ventricular rate is greater than 100/min, therefore ventricular rate > 160/min cannot be used to differentiate between ventricular & supraventricular tachycardia.***

| **Ventricular tachycardia** (Broad complex tachycardia) | **Supraventricular tachycardia** *(Narrow complex tachycardia)* |
|---|---|
| • Ventricular rate > 100 bpm | • Ventricular rates > 100 bpm [Q] |
| • QRS duration > 0.12 sec. (>.14 sec.- Harrison)[Q] | • QRS duration < 0.12 sec. |
| • Cannot be relieved by carotid sinus massage. [Q] | • Can be relieved by carotid sinus message [Q] |

**Other features can be used to distinguish ventricular and supraventricular tachycardia.**

- ***Variable First heart sound*** *is a features of ventricular tachycardia only.*
- *In ventricular tachycardia* ***QRS duration*** *is greater then 0.14 Sec, while in supra ventricular tachycardia it is less than 0.14 Sec.*
- *Supraventricular tachycardia can be relieved by* ***carotid sinus massage while ventricular tachycardia cannot.***

**115. Answer is C (Typical right bundle branch block):** *Harrisons 17th/ Braunwald 8th/898, Cardiology by 'Heger' 5th/52 Clevelend clinic cardiology board review (2006)/659 by Eric Topal ; Evidence based Medicine Guidelines (2005) / 112*

***Wide complex tachycardia due to ventricular tachycardia (VT) is characterized by bizzare QRS pattern that does not mimic typical RBBB or LBBB QRS complexes***

*The presence of wide QRS complex tachycardia with typical RBBB or LBBB suggests supraventricular tachycardia with aberrant conduction.*

Wide complex tachycardia (QRS duration >°12 seconds)

- Wide complex tachycardia is defined as tachyarrhythmia with a QRS duration greater than 0.12 seconds with a heart rate > 100/min
- Wide complex tachycardia may occurs as a result either from a ventricular (VT) or supraventricular mechanism (SVT with aberrancy)

Broad Complex Tachycardia

| Ventricular Tachycardia | Supraventricular Tachycardia with abberancy |
|---|---|
| VT is the most common cause of Broad complex tachycardia accounting for >80% of cases | SVT with abberancy accounts for 15-20% cases of broad complex tachycardia<br><br>Cause include<br>• SVT with a bundle branch block either LBBB or RBBB<br>• Atral flutter, Atrial fibrillation, AV reentrant tachycardia (AVRT) may also produce SVT with aberancy and result in wide complex tacycardia. |

Distinguishing Features between Broad complex tachycardia due to VT and SVT with aberrancy

| **Differentiating features** | **Ventricular Tachycardia** | **Supraventricular Tachycardia with Abaerrancy** |
|---|---|---|
| • *QRS duration* | *Broad complex Tachycardia with QRS duration usually greater that 0.14 seconds*<br>*QRS ≥ 0.14 sec* | *Broad complex tachycardia with QRS duration usually between 0.12 sec to 0.14 seconds*<br>*QRS ≤ 0.14 sec.* |
| • *Fusion Beats* | *Characteristic of VT* | *Absent* |
| • *Capture Beats* | *Characteristic of VT* | *Unusual* |
| • *AV dissociation* | *Characteristic of VT* | *Absent* |
| • *Independent P waves* | *May be seen*<br>*Independent P waves when present are characteristic of VT and indicate AV dissociation* | *Independent P work's are not seen*<br>*P wave and QRS complex are linked to suggest that ventricular activation depends on atrial discharge* |
| • *QRS pattern* | *QRS pattern does not resemble /mimic typical LBBB or RBBB* | *QRS pattern often resembles /mimics typical LBBB or RBBB* |
| • *Axis (Frontal plane QRS)* | *Left axis deviation (< - 30°)* | *Normal or Right ward* |
| • *QRS morphology in V1* | *Monophasic or Biphasic* | *Triphasic* |
| • *R/S Ratio in V6* | *<1* | *>1* |
| • *Vagal manuvres* | *No effect* | *Slowing or termination of tachycardia by vagal manuvres* |

**116. Answer is D (Termination of tachycardia by carotid sinus massage):** *Harrison's 18th/1888*

***Broad complex tachycardia from ventricular tachycardia is not terminated by carotid sinus massage.*** *Termination of tachycardia by carotid sinus massage suggests a broad complex tachycardia due to supraventricular tachycardia with aberrancy.*

**117. Answer is A, B, C (Fusion beats; Capture beats and AV dissociation):** *Refer previous question, Braunwald 8th/896, 897*

***Presence of Fusion beats, capture beats and AV dissociation is charachteristic of ventricular tachycardia.***

ECG feature that support a diagnosis of ventricular tachycardia (Vt) in patients with Wide Complex Tachycardia (Incomplete List)

- ***Presence of Fusion beats***
- ***Presence of capture beats***
- ***Presence of AV dissociation***

*The presence of fusion beats and capture beats provides maximum support for the diagnosis of VT. AV dissociation also provides a strong support in favour of VT, but is less specific than fusion beats and capture. AV dissociation may uncommonly occur during supraventricular tachycardias and all cases of VT may not exhibit AV dissociation. Never the less presence of AV dissociation in cases of wide complex tachycardia is a strong presumptive evidence that tachycardia is of ventricular origin (VT).*

| Differentiating features | VT (Broad complex) | SVT with Aberrancy (Broad Complex) |
|---|---|---|
| Fusion beats | Characteristic | Absent |
| Capture beats | Characteristic | Unusual |
| AV dissociation | Characteristic | Absent |
| Effect of vagal manuvres | No effect | Slowing or termination of tachycardia |
| QRS morphology in V1 | Monophasic or Biphasic | Triphasic |

**118. Answer is E (Typical RBBB QRS complex):** Harrison 18th/p 1892 *Harrisons 17th/1437 Kelly's Essentials of Medicine 2nd/133*

***Wide QRS complex, AV dissociation, capture beats, and fusion beats are characteristic features of ventricular tachycardia.***

*VT is characterized by bizarre QRS complexes that do not confirm to typical RBBB or LBBB QRS complexes*

**Ventricular Tachycardia** (VT)

VT is defined as ≥ three consequtive premature ventricular complexes with a wide QRS complex of duration ≥ 0.12 sec (often ≥ 0.14 sec) and a heart rate between 100 to 240/minute. The QRS complexes are not preceded by atrial deflections.

Characteristic Features of Ventricular Tachycardia (VT)

- *AV dissociation* Q
- *Capture Beats* Q
- *Fusion Beats* Q
- *Compensatory Pause* Q
- *Wide QRS complex (>0.14 seconds)* Q
- *Bizarre QRS pattern that does not mimic typical RBBB or LBBB QRS complex* Q
- *Left axis deviation* Q

Additional features

- Heart Rate : The heart rate is >100/minute (usually >120/min
- Rhythm : Usually Regular
  May be irregular if there are sinus capture beats
- P:QRS : No fixed relation exists between the P wave & QRS complex
  - *P wave may not be visible at all*
  - *P wave may be dissociated from the QRS complex*

**119. Answer is C (Prevalence decreases with age):** *Braunwald 8th/895*

*The presence of premature complexes increases with age – Braunwald 8th/895*

Premature Ventricular Contractions or Premature Ventricular Complexes (VPC's)
(Ventricular Premature Beats, Ventricular Ectopic beats)

- Premature ventricular contractions / complexes are caused by an ectopic impulse that originates in the purkinje fibres distal to the bifurcation of the bundle of His, or in the working ventricular myocardium
- Such ectopic impulses arising from the ventricles do not enter the conducting pathway and hence do not depolarize both ventricles simultaneously but cause sequential depolarization of ventricles, one ventricle at a time
- Such sequential depolarization results in abnormal conduction of impulse and causes a wide bizarre QRS complex (> 0.12 sec)

Characteristics of PVC's (ECG)

- *The QRS complex is premature* Q
- ***The QRS complex is wide (>0.12 sec)*** Q ***and BIZZARE*** Q ***or distorted (notched)***
- *The QRS complex is not preceded by a P wave* Q
- *A' P' wave is not associated with the PVC* Q
- *The QRS complex is usually followed by a complete compensatory pause* Q
  *(The compensatory pause following PVC is frequently complete)* Q
- *The QRS complex may be monophasic or biphasic (Not Triphasic)* Q
- *The ST segment and T wave slope in the opposite direction from the main deflection of the QRS complex.* Q

Clinical features

- ***The prevalence of PVC increases with Age***
- They are associated with male gender (Male > Females)
- May occurs in patients with no cardiovascular abnormalities and in patients with underlying cardiovascular disease
- Majority of patients are asymptomatic
- *Presenting symptoms include* ***palpitations****, lightheadedness, fatigue, near syncope, syncope*

Prognosis

*In presence of coronary artery disease (CAD) or history of MI, complex or frequent VPC's are associated with increased risk of sudden cardiac death.*

**120. Answer is D (Prolonged PR interval):** Harrison 18th/p 1892 *Braunwald 8th/893-898, Harrisons 17th/1437, CMDT 2008/334, Cardiology' 5th/51,52*

*PR interval does not characterize Ventricular Premature complexes because AV conduction is not involved.*

*Wide QRS complex, Absent P wave and a frequently Complete Compensatory Pause are all characteristic features of Premature ventricular complexes.*

**The basic ECG characteristics of PVCs include the following:**

| | |
|---|---|
| Rate | The underlying sinus rate is usually regular but is intermittently interrupted by the PVC. This results in an irregular and fluctuating heart rate. |
| Rhythm | The basic R-R interval is regular but is intemittently interrupted by the PVC. The R-R interval preceding the PVC is short due to the "prematurity" of the QRS complex and often the R-R interval after the PVC is longer due to a compenstory pause (Fig.2) |
| P wave | The premature QRS complex is not preceded by a conducted P wave (although in certain instances the PVC may coincidentally be preceded by a nonconducted sinus P wave) |
| PR interval | Not applicable because atrioventricular (AV) conduction is not involved. |
| QRS complex | *QRS complex is premature* Q<br>*QRS complex is prolonged (>0.12 seconds)* Q<br>*QRS complex is bizzare or distorted (notched)* Q<br>*QRS complex is not proceeded by a P wave* Q<br>*QRS complex is frequently followed by a complete compensatory pause* Q |
| ST segment and T wave | *The ST segment and T wave slope in the opposite direction from the main deflection of QRS complex* Q |

Note

*'AV dissociation' with 'capture beats' and 'fusion beats' are diagnostic criteria for ventricular tachycardia (VT) and not for PVC's.*

*However, VT is defined by the presence of three or more consecutive PVC and hence AV dissociation, capture beats and fusion beats may be said to be occasionally present in PVC's when they occur in consecutive bests.*

**121. Answer is D (Wide QRS complex):** *Harrison 18th/p 1890Kelly's Essentials of Internal Medicine 2nd/133; Harrison 18th/p 1890 Harrison's 17th/1435, Braunward 8th/896, 897; CMDT 2009/341*

***Wide QRS complex (>12sec) is characteristic of Premature ventricular beats***

*Presence of AV dissociation with fusion beats and capture beats is considered diagnostic for Ventricular Tachycardia and not PVC.*

*However, VT is defined by the presence of three or more than three ventricular premature beats (PVC) in succession and hence AV dissociation, Fusion beats and capture beats may be said to be present in PVC's also (provided PVCs occur in quick succession).*

| AV dissociation | Fusion Beats | Capture beats |
|---|---|---|
| The prevence of AV dissociation implies that atrial and ventricular activity are occurring in dependent of each other<br>AV dissociation can occur in patients with ventricular tachycardia and retrograde conduction block<br>The presence of AV dissociation favours a diagnosis of VT | • Fusion beats result from activation of ventricle by two foci, one supraventricular and the other ventricular<br>• The presence of fusion beats supports a diagnosis of VT | • Capture beats indicate activation of the ventricle by a conducted supraventricular rhythm resulting in a shorter coupling interval and a QRS of normal morphology<br>• The presence of capture beats favours a diagnosis of VT. |

**122. Answer is B (Narrow QRS complex):** *Kelly's Essentials of Internal Medicine 2nd/133;* Harrison 18th/p 1890 *Harrison's 17th/1435, Braunward 8th/896, 897; CMDT 2009/341*

***Premature Ventricular beats are characterized by a wide QRS Complex and not a narrow QRS complex.***
*AV dissociation, Fusion beats and capture beats may be observed when three or more than three PVC's occur in succession.*

**123. Answer is B (Myocardial Reperfusion):** *ACS Essentials '2010' 3rd (2009) /132,* Harrison 18th/p 1890 *Harrisons 17th/1435, 1436; Hurst12th/ 1014; Braunwald 8th/-864-865-895-896-1278; 'Problem Oriented Approach in Interventional Cardiology' by Colombo (2007)/109*

***Accelerated Idioventricular Rhythm is the most common arrhythmia seen after successful reperfusion of a blocked coronary vessel and hence is often also termed as a 'reperfusion rhythm or reperfusion arrhythmia'.***

*'Arrhythmias are common after reperfusion. The most common post reperfusion arrhythmia is Accelerated Idioventricular Rhythm (AIVR)' - Problem Oriented Approach in Interventional Cardiology*

*'Accelerated Idioventricular Rhythm is considered a reperfusion rhythm as it is often seen immediately after a successful reperfusion' - Washington manual of critical care /116*

***Myocardial Reperfusion, Dilated cardiomyopathy, Digitalis matoxication and Myocarditis** may all produce Accelerated Idioventricular Rhythms (AIVR), however AIVR is the most common arrhythmia seen after myocardial Reperfusion. AIVR is also the most charachteristic aryhythmia seen after reperfusion has begun and **hence Myocardial Reperfusion is the single best answer of choice.***

**Accelerated Idioventricular Rhythm (AIVR)**

- AIVR is an automatic rhythm originating within the ventricle with rates between 40 to 120 beats / min
- AIVR is believed to be caused by abnormal automaticity and is considered to be a brief self limiting arrhythmia , that does not usually require any specific treatment unless the patient is symptomatic

- The onset of this arrhythmia is gradual (non paroxysmal) and occurs when the rate of ventricular tachycardia exceeds the sinus rate because of sinus slowing or SA / AV block
- ***AIVR is a characteristic feature of myocardial reperfusion, and when it occurs in the setting of myocardial infarction and coronary reperfusion it is also called 'Reperfusion Arrhythmia' or 'Reperfusion Rhythm'.***
  *'It commonly occurs at the moment of reperfusion of an occluded coronaryartery' – Braunwald*
- AIVR can be seen in the absence of any structural heart disease but is usually seen in patients who have an underlying structure heart disease.

**Causes of Accelerated Idioventricular Rhythm (AIVR)**

- Acute coronary syndromes
  - Acute Myocardial Infarction
  - ***Myocardial Reperfusion***
- Cardiomyopathy
  - *Dilated cardiomyopathy*
  - Ischemic cardiomyopathy
- *Myocarditis* (Acute myocarditis)
- Rheumatic / Congenital Heart Disease
- **Digitalis Intoxication** (*AIVR is **not** the most common arrhythmia seen after Digitalis toxicity*)
- Cocaine Intoxication

*'Arrhythmias are common after Reperfusion. The most common post reperfusion arrhythmia is Accelerated Idioventricular Rhythm'*
*- Interventional cardiology*

**Electocardiographic features of Accelerated Idioventricular Rhythm (similar to VT except ventricular rate)**

- *Rate , 40 to 120 beats / min*
- *Wide QRS complex (> 0.12 sec) (Bizzare)*
- *Fusion beats*
- *Capture beats*
- *AV dissociation*
- *Rhythm: Regular*

*Although the ventricular rate in AIVR by definition can be upto 120 beats / min, this is usually less than 100/min. A rate between 100 to 120 may represent VT and hence should be treated as VT.*

**Treatment of Accelerated Idioventricular Rhythm**

**No specific treatment is usually required (No treatment in Asymptomatic patients)**
Since the ventricular rate usually ranges the same as sinus rhythm, hemodynamic compromise does not occur Also the condition is self limiting and transient and does not appear to affect the patients clinical course or prognosis.
Hence no specific treatment is required although these patients should be observed

**Symptomatic patients with Hemodynamic compromise may require treatment**
- Atropine or Atrial pacing may suppress the AIVR by simply increasing the sinus rate
- Lidocaine may be used for suppressive therapy

## Torsades De Pointes

**124. Answer is C (Prolonged QTc interval):** Harrison 18th/p 1890 *Harrison 15th/1304, 16th/1353; 17th/1436; CMDT 2008/334; CMDT 2009/341*

***'The ECG hallmark of torsades depoint's is marked QT prolongation'.***

***'Torsades de pointes' or 'twisting of the points'*** is a specific type of ventricular tachycardia

**Characteristics of *Torsades de pointes***
- Polymorphic QRS complexes that change in amplitude
- Cycle length giving the appearance of oscillations around the baseline.
- Marked QT prolongation $^{Q}$

**125. Answer is B (polymorphic Ventricular Tachycardia):** Harrison 18th/p 1891 *Hurst 12th/1082,1083*

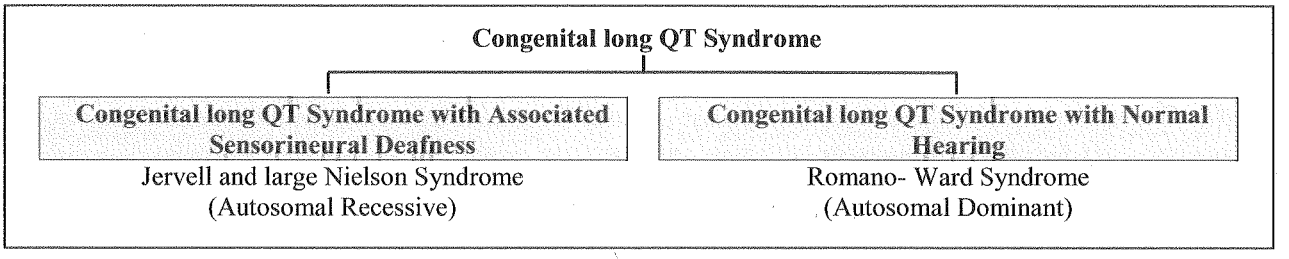
***Torsades de pointes is the hallmark arrythymia in the long QT syndrome*** – *Hurst 12th/1016*
***Pylomorphic ventricular tachycardia is synonymous with Torsades de Pointes and the single best answer of choice.***

*Congenital long QT Syndrome is associated with reduced repolarization reserve. Reduced repolorization reserve predisposes patients with marked QT prolongation to develop Torsades de pointes.*

*- Hurst 12th/1082,1083*

**What is congenital long QT Syndrome**

Congenital long QT Syndrome is a familial disorder characterized by a prolonged QT interval on Electrocardiogram
Most forms of congenital long QT Syndromes are caused by Channelopathies created by mutations in one or more genes




How do Patients with congenital long QT Syndrome present

- *May present with syncope due to* ***torsades de pointes***[Q]
- *May present with sudden death due to* ***ventricular fibrillation***[Q]

Note

Ventricular Tachyarrythmias commonly develop during periods of adrenergic stimulation such as fright or exertion but may also develop during sleep.
Most competitive sports are contraindicated for patients with congenital long QT syndrome

**Clinical conditions that are associated with reduced repolarization reserve (Patient predisposed for marked QT prolongation and resultant Torsades-de pointes)**

- *Congenital long QT Syndrome*
- *Acquired long QT Syndrome caused by a variety of drugs/ medications*
- *Bradycardia*
- *Female gender*
- *Ventricular Hypertrophy*
- *Electrolyte disturbances such as hypokalemia and hypomognesemia*

**126. Answer is C (Hypomagnesemia):** Harrison 18th/p 1891 *Hurst 12th/1082, 1083, 1016 Refer previous question*

***Electrolyte disturbances including hypomagnesemia predispose patients for marked QT prolongation and Torsades – des – pointes as a result of reduced repolarization reserve.***

Clinical conditions associated with reduced repolarization reserve
(Patients predisposed for marked QT prolongation and Torsades –de pointes)

- *Congenital long QT syndrome*
- *Acquired long QT syndrome (caused by variety of drugs /medications)*
- ***Electrolyte disturbances such as hypokalemia and hypomagnesemia***
- *Ventricular Hypertrophy*
- *Female gender*

## WPW Syndrome

**127. Answer is B (Right sided accessory pathway):** *Refer text below*

*Wolf Parkinson White syndrome is caused by the presence of on additional / accessory pathway (connection) between the atria and ventricle. The acessary pathway (called bundle of Kent) may be present as a connection between the left atrium and left ventricle (Left sided) or as a connection between the right atrium and right ventricle (Right sided).*

Pre excitation resulting from left sided accessory pathways is called Type A Pre-excitation
Pre excitation resulting from right sided accessory pathway is called Type B Pre-excitation

***The most common accessary pathways leading to pre-excitation syndromes (WPW) are left sided (connecting left atrium to left ventricle)***[Q]

**128. Answer is A (Left free wall):** *Harrison 18th /1889; Braunwald Heart Diseases Review & Assessment' by Lilly (Elsevier) 2012/Q 249*

***Left free wall accessory pathways are most common.***

*'Left free wall accessary pathways are most common followed by posteroseptal, right free wall and anteroseptal locations' -'Braunwald Heart Diseases: Review & Assessment' by Lilly (2012)/Q249*

*'The most common accessary pathway connects the left atrium to the left ventricle followed by posterior septal, right free wall and anterior septal accessary pathways' – Harrison's 18th/1889*

**129. Answer is A (Orthodromic AV reentry):** *Harrison 18th/1889*

***The most common macro-reentrant tachycardia associated WPW syndrome is orthodromic AV reentry.***

*'The most common macro-reentrant tachycardia associated with WPW syndrome is referred to as Orthodromic AV reentry' – Harrison's 18th/1889*

**130. Answer is A (Narrow QRS complexes):** Harrison 18th/p 1889 *Harrison 16th/1350, 17th/ 1434; ECG made easy by John R Hampton 8th*

*WPW syndrome is characteristically associated with a wide QRS complex.*

**WPW Syndrome : Features**

- *Wolf Parkinson White syndrome is caused by the presence of on additional / accessory pathway (connection) between the atria and ventricle.* Normally the AV node is the only pathway that allows electrical connection between atria and ventricles and allows some delay in conduction of impulses from atrial to ventricles.
  *Accessory bundles do not have an AV node to delay conduction and form such a direct connection between atrium and ventricle – This constitutes WPW syndrome.*
- A depolarization wave reaches the ventricle early and causes premature excitation of ventricles – *preexcitation.* Q
- *Paroxysmal tachycardias* Q *are produced as a result of such preexcitation.*
- *The acessary pathway (called bundle of Kent) may be present as a connection between the left atrium and left ventricle (Left sided) or as a connection between the right atrium and right ventricle (Right sided).*

  *Pre excitation resulting from left sided accessory pathways is called Type A Pre-excitation*
  *Pre excitation resulting from right sided accessory pathway is called Type B Pre-excitation*
- ***The most common accessary pathways leading to pre-excitation syndromes (WPW) are left sided (connecting left atrium to left ventricle)*** Q

  ***Left free wall accessory pathways are most common.***
  *'Left free wall accessary pathways are most common followed by posteroseptal, right free wall and anteroseptal locations' -'Braunwald Heart Diseases: Review & Assessment' by Lilly (2012)/Q249*
- ***The most common macro-reentrant tachycardia associated WPW syndrome is orthodromic AV reentry.***
  *'The most common macro-reentrant tachycardia associated with WPW syndrome is referred to as Orthodromic AV reentry' – Harrison's 18th/1889*
- ***WPW Syndrome has a charachteristic ECG Patern***

  **Typical ECG pattern includes**
  - *Short PR interval* Q
  - *Slurred upstroke of QRS complex* Q *i.e. Delta wave.*
    *The second part of QRS complex is normal as conduction through bundle of His catches up with preexcitation.*
  - *Wide QRS complex* Q

**131. Answer is A, E (More common in females and Incidence is 0.3 to 0.7%):** *Braunwald 8th/890, 884*

***WPW syndrome is more common in males and the incidence varies from 0.1 to 3/1000 in apparently healthy subjects (i.e 0.01 to 0.3 percent)***

**WPW syndrome : Accessory AV Pathways**

- WPW syndrome or 'Prexcitation syndrome' is charachterized by the presence of *tachyarrythmias*[Q] due to an *accessory conducting pathway*[Q] between atrium and ventricle
- WPW abnormality occurs when an impulse reaches the atria or ventricles earlier than would be expected if the impulse traveled by way of normal specialized conducting tissue *(Pre excitation)* [Q]

| |
|---|
| - When atrial impulse activates the entire or some part of ventricle<br>- When ventricular impulse activates the entire or some part of the atrium |

Epidemiology

- ***Incidence varies from 0.1 to 3.0/1000 in apparently healthy subjects (Average = 1.5/1000)***
- It may be found in all ages (Neonates to Elderly)
- Prevalence decreases with age apparently because of loss of preexcitation
- ***It is more common in Males***
- Most adults with WPW syndrome have normal heart
  (However various acquired and congenital defects may be associated specially Ebstein's anomaly, MVP and cardiomyopathics)

Electrocardiographic features

Three basic features typify the ECG abnormalities with usual form of WPW syndrome

- Short PR interval (PR interval <120 ms during sinus rhythm)[Q]
- Wide QRS complex (>120 ms) with a slurred slowly rising upstroke (delta wave) [Q]
  *The terminal portion of QRS complex is usually normal as conduction through bundle of His usually catches up with preexcitation*
- Secondary ST-T changes[Q] that are generally directed to an opposite direction to the major Delta/ QRS vectors

**Note**

- **Fusion beats**: [Q] If the accessory pathway is capable of anteprade conduction, the typical QRS complex represents a 'Fusion beat' as a result of depolarization of the ventricle in part by the wave travelling from the accessory pathway and in part by wave travelling from normal AV nodal pathway
- **Normal p wave**[Q] – Since the atrial activation is normal, the P wave is usually normal

**132. Answer is B (Procainamide):** *Hurst 12th/981*

***Intravenous Procainamide is recommended to restore sinus rhythm in patients with Atrial fibrillation associated with the WPW syndrome.***
***Procammide is the single best answer amongst the options provided.***

Management of Atrial fibrillation with WPW Preexcitation Syndrome: Recommendations

1. Catheter ablation of the accessory pathway is recommended in symptomatic patients with AF who have WPW syndrome, particularly those *with syncope due to rapid heart rate or those with a short bypass tract refractory period.*
2. Immediate direct-current cardioversion is recommended to prevent ventricular fibrillation in patients with a *short anterograde bypass tract refractory period in whom AF occurs with a rapid ventricular response associated with hemodynamic instability.*
3. **Intravenous procainamide or ibutilide** is recommended to restore sinus rhythm *in patients with WPW in whom AF occurs without hemodynamic instability in association with a wide QRS complex on the electrocardiogram* (ECG) (greater than or equal to 120-ms duration) or with a rapid preexcited ventricular response.

**133. Answer is A (Verapamil):** *Harrison 18th/ 1890*

***AV nodal blocking agents such as Calcium channel blockers, Beta blockers and Digoxin should not be used to treat Atrial Fibrillation in patients with WPW Syndrome.*** *Use of these drugs may result in an acute increase in rate over the Accessory pathway placing the patient at risk for development of VF.* ***Procainamide is the drug of choice for treatment of Atrial Fibrillation in patients with WPW Syndrome who are hemodynamically stable. Ibutilide and Amiodarone are also effective.***

**Treatment of Hemodynamically Stable Atrial Fibrillation in Patients with WPW Syndrome**

- Procainamide is the drug of choice for treatment of Atrial Fibrillation in patients with WPW Syndrome who are hemodynamically stable.

- Ibutilide and Amiodarone are also effective.
- Avoid AV nodal blocking agents such as Calcium channel blockers, Beta blockers and Digoxin

*The standard treatment of atrial fibrillation is to slow the ventricular rate with AV nodal blocking agents such as Calcium channel blockers, Beta blockers and Digoxin. In Patients with Pre-excitation (WPW Syndrome) the use of these agents should be avoided (contraindicated). Atrial Fibrillation in patients with WPW Syndrome is typically associated with rapid conduction over the AV node as well as the Accessory Pathway. AV nodal blockers slow down conduction and decrease the number of impulses entering the ventricles anterogradely through the AV node (but may increase the rate of conduction through the accessory pathway). This will reduce the number of impulses bombarding the ventricular end of the bypass tract or accessory pathway rendering the bypass tract less refractory. This may paradoxically increase the rate of conduction through the accessory pathway placing the patient at risk for development of VF.*

*'Digoxin appears to shorten the refractory period of the Accessory pathway directly and thus increases the ventricular rate' - Harrison*
*'Verapamil appears to shorten the refractory period of the accessory pathway indirectly by causing vasodilatation and a reflex increase in sympathetic tone' – Harrison*

**134. Answer is C (DC Cardioversion):** *Harrison 18th / 1890*

***DC Cardioversion is the treatment of choice to terminate Atrial Fibrillation in patients with WPW Syndrome who are hemodynamically unstable (Life threatening Situations).***

**135. Answer is C (WPW):** *Harrison 18th/p 1889, 1890; Harrison 17th/ 1415, 1434, 1435*

***'Ablation of bypass tract offers a permanent cure of supraventricular tachycardias. The advent of radiofrequency catheter ablation has virtually eliminated the need for surgery.'*** *– Harrisons*

## Heart block and Conduction Disturbance

**136. Answer is C (Less than 60/min)**

***Sinus bradycardia can be defined as a sinus rhythm with a resting heart rate of 60 beats per minute or less.***

**137. Answer is A (Constant PR interval):** *Refer text below*

***Mobitz Type I block (second degree: Wenchebach type) is characterized by a variable PR interval, (PR interval is not constant). PR interval in type I block characteristically gets longer until a QRS complex is dropped***

### First Degree AV Block

First degree AV block is charachterized by a delay in conduction across the conducting tissue (prolonged PR interval)

**Features**

- *PR interval is prolonged (>0.20 seconds)* Q
- *PR interval is constant (at the prolonged duration)* Q
- *Rhythm is regular* Q
- *Each P wave is followed by a QRS complex* Q
- *QRS complex morphology / duration is usually normal* Q

### Second Degree AV Block

Second degree AV block is characterized by intermittent failure of conduction from atria to ventricles

#### Type I (Mobitz) / Wenchebeck Type

This is charachterized by progressive prolongation of PR interval prior to a non conducted P wave

**Features**

- *Atrial Rhythm regular* Q
- *Ventricular Rhythm irregular* Q
- *Atrial rate exceeds ventricular rate* Q
- *PR internal varies* Q
- *PR progressively gets longer until a QRS is dropped* Q
- *QRS morphology is often normal* Q

#### Type II (Mobitz)

This is charachterized by constant PR interval prior to a non conducted P wave

**Features**

- *Atrial Rhythm regular* Q
- *Ventricular Rhythm Regular (unless conduction rations vary)* Q
- *Atrial Rate exceeds ventricular rate* Q
- *PR interval is constant* Q
  *PR interval does not get progressively longer and a QRS is dropped suddenly*
- *QRS morphology is usually abnormal* Q *(rarely normal)*

**Third Degree AV Block: Complete AV Block**

Third degree AV block or complete AV block is charachterized by complete failure of conduction from atria to ventricles. (Atria and ventricles are under the control of separate pacemakers).

**Features**

- *Atrial Rhythm regular* $^{Q}$
- *Ventricular Rhythm regular* $^{Q}$
- *Atrial rate exceeds ventricular rate* $^{Q}$ *(The inherent rate of ventricular pacemaker is slower)*
- *PR interval varies* $^{Q}$ *(variable)*
- *P waves have no constant relationship to QRS complexes* $^{Q}$ *(AV dissocation)*
- *QRS complex morphology may be abnormal* $^{Q}$

**138. Answer is A, C (First –Degree block and Second Degree Mobitz type II):** *Refer text below*

***First degree Heart block and second degree Mobitz type II block are associated with constant PR interval.***

**PR Interval**

| Constant | Variable |
|---|---|
| • First degree block<br>• Second Degree – Mobitz II | • Second degree – Mobitz I<br>• Third degree block |

| **PR constant (First-degree)**<br>**(First-degree)** | **PR varies**<br>**(Second-degree, Mobitz 1)** |
|---|---|
| *PR constant* | *PR varies* |
| *PR prolonged* | *PR progressively gets longer until a QRS is dropped* |
| *Regular atrial rhythm;*<br>*Regular ventricular rhythm* | *Regular atrial rhythm;*<br>*Irregular ventricular rhythm* |
| **(Second –degree, Mobitz II)** | **(Third- degree)** |
| *PR constant* | *PR varies* |
| *PR normal or prolonged*<br>*Two or three P waves (possibly more) to each QRS* | *P waves have no constant relationship to QRS (found hidden in QRS complexes and T waves)* |
| Regular atrial rhythm;<br>Regular ventricular rhythm (unless conduction ratios vary) | *Regular atrial rhythm;*<br>*Rgular ventricular rhythm* |

**139. Answer is A, B, and C:** *Hurst 12th/1029, 1030; ECG Workbook by Huff 5th/155*

***Second degree AV block (Type I and /or Type II) may be associated with prolonged conduction time (prolonged PR interval), Atrial rate more than ventricular rate and change in QRS complex morphology (Type II).***

| Name | Rhythm | Rate (beats/minute) | P waves (lead II) | PR Interval | QRS complex |
|---|---|---|---|---|---|
| First-degree atrio-ventricular (AV) block | Regular | That of underlying sinus rhythm; both atrial and ventricular rates will be the same | ***Sinus origin; one P wave to each QRS complex*** | Prolonged (more than 0.20 second); remains constant | Normal (0.10 second or less) |
| Second-degree AV block, Mobitz I | Atrial: regular<br>Ventricular: irregular | Atrial: that of underlying sinus rhythm<br>Ventricular: depends on number of impulses conducted through AV node: ***will be less than atrial rate*** | Sinus origin | Varies; progressively lengthens until a P wave isn't conducted (P wave occurs without the QRS complex); a pause follows the dropped QRS complex | Normal (0.10 second or less) |
| Second-degree AV block, Mobitz II | Atrial: regular<br>ventricular: usually regular, but may be irregular if | Atrial: that of underlying sinus rhythm<br>Ventricular: depends | Sinus origin: two or three P waves (sometimes more) before each QRS | Normal or prolonged; remains constant | Normal if block at level of bundle of His;<br>***Wide if block in*** |

| | | | | | |
|---|---|---|---|---|---|
| | conductions ratios vary | on number of Impulses conducted through AV node; will be ***less than atrial rate*** | complex | | ***bundle branches*** |
| Third-degree AV block | Atrial: regular<br>Ventricular: regular | Atrial: that of underlying sinus rhythm<br>Ventricular:40 to 60 if paced by AV junction; 30 to 40 (sometimes less) if paced by ventricles; will be less than atrial rate | Sinus P waves with ***no constant relationship to the QRS complex***; P waves found hidden in QRS complexes and T waves | Varies greatly | Normal if block at level of AV node or bundle of His; wide if block in bundle branches |

*No constant Relationship between P wave and QRS complex is a feature of Third degree or complete heart block.*
*One P wave to each QRS complex is a feature of First degree block*

**140. Answer is D (Seen in digitalis toxicity with $K^+$ depletion):** *Harrison 18th/p 1897; 17th/ 1441*

***Nonparoxysmal atrial tachycardia with variable AV block is characteristic of digitalis intoxication. Depletion of potassium stores is one of the most common precipitating cause of digitalis intoxication. Presence of potassium depletion in association with digitalis is thus likely to result in manifestations of digitalis toxicity.***

**141. Answer is a (Cardiac Surgery):** *Park' Pediatric Cardiology for Practitioners (Elsevier) 6th/ 251; Mayo Clinic Cardiology: Concise Textbook (Oxford University Press) 4th /269*

***Cardiac surgery is the most common cause of acquired complete heart block in children.***

> ***'Cardiac surgery is the most common cause of acquired complete heart block in children'***
> - *Park' Pediatric Cardiology for Practitioners*
>
> ***'Postsurgical third-degree AV block, resulting from trauma to the AV node at operation, is the most common cause of acquired AV Block in children'*** - *Mayo Clinic Cardiology: Concise Textbook*

**142. Answer is D (Diltiazem):** Harrison 18th/p 1867, 1874 *Harrison 16th/1348, 1339; Harrison 17th/ 1416-1422*

***Diltiazem is used in the treatment of tachyarhythmias and not in the treatment of bradyarrhythmias.***

*Diltiazem is a class IV antiarrhythmogenic drug, used in atrial fibrillation/flutter and supraventricular tachycardias (tachycardias) to slow the ventricular rate, by decreasing conduction velocity and increasing refractoriness in the AV nodal tissue.* ***Atropine, Isoproterenol and pacemakers are all useful in the management of bradycardia.***

- ***Atropine*** and ***isoproterenol*** are useful in increasing heart rate and decreasing symptoms in patients with sinus ***bradycardia*** or AV block localized to AV node.' - *Harrison 16th/1339*
- Long term therapy of brady arrhythmias is best accomplished by ***pacemakers***. - *Harrison 16th/1339*

**Management of Bradycardias :** Oxford hand book of Medicine : *6th/126*

**Bradycardia**

| Rate > 40 bpm<br>Asymptomatic | Rate < 40 bpm<br>Symptomatic |
|---|---|
| No treatment<br>Look for cause and<br>Treat contributing factor | • Atropine<br>↓ No response<br>• ***Temporary pacing wire*** *If necessary start* ***isoprenaline*** *infusion or use external cardiac* ***pacing.*** |

## Athletic Syndrome

**143. Answer is D (Shortened $QT_C$ Interval):** *Sports Cardiology: From Diagnosis to Clinical Management (Springer) 2012/ 18,19; Clinical Approach to Sudden Cardiac Death Syndromes (Springer) 2010/ 60; ACSM's Sports Medicine: A Comprehensive Review(Lippincott Williams & Wilkins) 2012 /173; Practical ECG for Exercise Science and Sports Medicine/132;*

***Athletes Heart is associated with a prolonged QT Interval and not a shortened QT interval.***
***Athlete's heart is usually associated with a prolonged QT interval because of bradycardia. When corrected for heart rate the QT Interval ($QT_C$) is usually at the upper limit.***

| Common ECG findings in Athletic Heart syndrome | |
|---|---|
| • *Sinus bradycardia* | • *RVH by voltage criteria (High QRS Voltage)* |
| • *Sinus arrhythmia* | • *LVH by voltage criteria (High QRS Voltage)* |
| • *First-degree AV block* | • *Early repolarization changes* |
| • *Second Degree Heart Block (Mobitz 1; Wenckebach AV block)* | • *Prolonged QT Interval (Due to bradycardia)* |
| • *Incomplete RBBB* | • *QTc interval at upper limit ($QT_C$ is QT Interval corrected for Heart Rate)* |
| • *Notched p waves (increase in amplitude and duration)* | • *Tall, Peaked T waves* |
| | • **Prominent U Waves** |

*AV, atrioventricular; ECG electrocardiogram; LVH . left ventricular hypertrophy; RBBB right bundle branch block RVH, right ventricular hypertrophy;*

**144. Answer is B (Second Degree (Mobitz 2) heart block):** *Sports Cardiology: From Diagnosis to Clinical Management (Springer) 2012/ 18,19; Clinical Approach to Sudden Cardiac Death Syndromes (Springer) 2010/ 60; ACSM's Sports Medicine: A Comprehensive Review(Lippincott Williams & Wilkins) 2012 /173; Practical ECG for Exercise Science and Sports Medicine/132;*

***Second Degree (Mobitz 2) heart block should be considered a pathological finding in an Athletes Electrocardiogram.***
*'Various degrees of atrioventricular blocks have been described in endurance athletes. First Degree Blocks and Second Degree (Mobitz Type- 1) are a common finding. However second degree (Mobitz type -2) and third degree blocks are pretty rare and should be considered pathological'*
*- Sports Cardiology: From Diagnosis to Clinical Management (Springer) 2012/ 18, 19*

**The athletic heart syndrome**

| Benign findings | Pathologic findings |
|---|---|
| **Physical exam** | **Physical exam** |
| • Grades 1 and 2 systolic ejection murmurs | • Systolic murmurs at the lower sternal border augmented by Valsalva and decreased with squatting |
| • Split S2 | • Diastolic murmurs |
| • S3 or S4 | |
| **ECG changes** | **ECG changes** |
| • Sinus arrhythmia | • Down-sloping ST-segment depression |
| • Sinus bradycardia | • ST elevation with broad T waves |
| • ***First-degree heart block*** | • Significant Q waves (anterior or inferior pattern) |
| • ***Second-degree heart block (Mobitz 1)*** | • Delta waves (Wolff-Parkinson-white) |
| • Junctional escape beats | • ***Second-degree heart block (Mobitz 2)*** |
| • Voltage criteria for hypertrophy (High QRS Voltage) | • ***Third-degree heart block*** |
| • Early repolarization | • ***Prolonged QTC interval*** |
| • Incomplete right bundle branch block | • LVH with ST-T wave strain pattern |
| • P wave increases in amplitude and duration | |
| • Tall peaked T Waves | |
| • T-wave flattening for inversion that normalizes with exercise | |
| • Prominent U waves | |

*These findings assume an asymptomatic athlete. If an athlete is symptomatic or a possible pathologic finding is found further workup is indicated.*

**145. Answer is C (Prolonged QTc Interval):** *Sports Cardiology: From Diagnosis to Clinical Management (Springer) 2012/ 18,19; Clinical Approach to Sudden Cardiac Death Syndromes (Springer) 2010/ 60; ACSM's Sports Medicine: A Comprehensive Review(Lippincott Williams & Wilkins) 2012 /173; Practical ECG for Exercise Science and Sports Medicine/132;*

***A Prolonged QT Interval that is corrected for heart rate (Prolonged $QT_C$) in an athlete should be considered pathological and evaluated further.*** *Prolonged QT interval is a normal finding in professional athletes and is often seen due to the presence of bradycardia. The presence of prolonged QT interval corrected for heart rate ($QT_C$) is however unusual. The presence of prolonged $QT_C$ Interval should be considered pathological and evaluated further*

**Athlete's heart is usually associated with a prolonged QT interval because of bradycardia.**
*Professional athletes should be evaluated further for Identification of a prolonged QT Interval corrected for heart rate ($QT_C$). $QT_C$ interval at upper limit is a common finding in athletes, however the presence of a significantly prolonged $QT_C$ interval in athletes should be considered a pathological finding and evaluated further to exclude Congenital Long QT Syndrome (LQTS).*
Congenital Long QT Syndromes (LQTS) *are a recognized cause of adrenergic mediated polymorphic ventricular tachycardia and has been implicated in exercise related sudden cardiac death in young athletes. The identification of a prolonged QT interval corrected for heart rate ($QT_C$) should be considered pathological and evaluated further.*

**146. Answer is A (Increased amplitude of QRS complex):** *'The 5 Minute Sports Medicine Consult' (2001) /378*

***Increased amplitude voltage of QRS complex is a frequent finding in Athletic Heart Syndrome***

**Athletic Heart Syndrome**

- Athletic Heart Syndrome is a benign condition consisting of physiologic adaptations to the increased cardiac workload of exercise in trained athletes
- It represents a constellation of clinical findings that are the result of normal physiologic adaptation to strenuous physical activity
- In response to the increased physical demand, the left ventricles dilates and wall thickness increases. The mass to volume ratio however does not change

Physical examination

- *Decreased body fat and increased muscle mass (generally very physically fit)*
- *Pulse slow and often irregular (sinus bradycardia or bradycardia with first-and second-degree blocks)*
- *Grade I or II mid-systolic murmurs (benign functional ejection murmur resolves with valsalva maneuver)*
- *Third and fourth heart sounds very common benign filling sounds)*
- *Blood pressure typically remains normal*

Electrocardiogram rhythm

- Rhythm
  - ***Sinus bradycardia*** of 40 to 55 beats /min while at rest
  - Sinus pauses of more than 2.0 seconds due to increased vagal tone
  - Wandering atrial pacemaker, found only in dynamic athletes
  - First degree atrioventricular block present only at rest; P-R interval normalizes with exercise
  - Second degree atrioventricular block present only at rest: Mobitz I (wenckebach block) common in marathon runners; Mobitz II rare in athlete's heart.
- ***Voltage: ↑QRS voltage (Amplitude)***
  - Left ventricular hypertrophy found in 85% of olympic marathon runners
  - Right ventricular hypertrophy common in dynamic athletes but rarely seen in sedentary controls and static athletes sedentary control and static athletes
- Repolarization
  - S-T segment elevation with peaked T waves, normalizes with exertion
  - S-T segment depression may be rarely found in athletes
  - T-wave inversion in lateral leads associated with interventricular septal hypertrophy in static athletes (can be normal finding in dynamic athletes)

Chest radiography

- Heart is globular in appearance, particularly in endurance athletes.
- Cardiomegaly (cardiothoracic ratio >0.50)

## Congestive Heart Failure and PCWP

**147. Answer is A (Increased PCWP):** *Hurst 12th/692, 'Heart failure' 1st/163, 164; Refer text below*

***Elevated Pulmonary capillary wedge pressure (↑ PCWP) is a feature of left sided heart failure and not right sided heart failure.***
*Failure of Right ventricle results in systemic congestion, and not pulmonary congestion and hence PCWP is not raised unless Right heart failure is caused secondary to Left sided failure.*

| Left heart failure | Right heart failure |
|---|---|
| • Left heart failure is defined as a clinical syndrome where the dominant feature is fluid congestion in the lungs (pulmonary) rather than in the systemic circulation | • Right heart failure is defined as a clinical syndrome where the dominant feature is fluid congestion in the systemic circulation. |
| • The pulmonary capillary wedge pressure is typically elevated (↑PCWP) | • The pulmonary capillary wedge pressure is normal (Normal PCWP) unless Right heart failure is caused secondary to left sided heart failure (↑ed PCWP) ***(PCWP is not elevated in isolated Right heart failure)*** |
| • Predominant symptoms are related to passive congestion of lungs and pulmonary edema | • Predominant symptoms are related to passive systemic congestion |
| • Dyspnea | • Peripheral Edema |
| • Orthopnea | • Ascitis |
| • Paroxysmal Nocturnal Dyspnea (PND) | • Congestive hepatomegaly (may be pulsatile) |
| • Cough with Pink Frothy Sputum | • Congestive splenomegaly |
| • Rales / Crackles | • Weight gain |
| | • Nocturia |
| | • Raised JVP |
| | • Positive Hepatojugular reflex |

**148. Answer is D (Normal JVP):** *Hurst 72th/692; 'Heart failure' 1st/163; Refer previous question*

***Right ventricular infarcts will cause failure of Right Ventricle resulting in systemic congestion and a Raised JVP.***

**149. Answer is D (Hepatomegaly):** *Harrison 15th/1323 (not a new edition); Family Medicine (Lange) 4th/450*

***Hepatomegaly is a minor Framingham criterion in CHF.***

**The Framingham Heart Study Criteria:**

| Major Criteria | Minor Criteria |
|---|---|
| • Paroxysmal nocturnal dyspnea<br>• Neck vein distension<br>• Rates<br>• Cardiomegaly<br>• Acute pulmonary edema<br>• S3 gallop<br>• Increased venous pressure (> 16 cm)<br>• Circulation time ≥ 25s<br>• Hepatojugular reflux positive | • Ankle edema<br>• Night cough<br>• Hepatomegaly<br>• Pleural effusion<br>• Vital capacity reduced by one third from predicted<br>• Tachycardia (≥ 120) |
| **Major or minor criterion** | |
| • Weight loss of more than 4.5 kg over 5 days in response to treatment | |
| **Definite CHF** | |
| • Two major criteria or one major and two minor criteria. | |

**150. Answer is A (Mitral Stenosis):** Harrison 18th/p 1931 *Harrisons 17th/-1467*

***Isolated Mitral Stenosis is not associated with Left Ventricular Hypertrophy***

**Isolated Mitral Stenosis is not associated with Left ventricular Hypertrophy**

The burden of Mitral Stenosis (from obstruction of flow across the mitral valve) is received by the left atrium followed by pulmonary circulation, right ventricle and right atrium in that sequence

*Left ventricle is off loaded and neither receives pressure overload nor volume overload and hence does not show any hypertrophy*

Pathophysiological overload features from Mitral Stenosis may results in

- *Left Atrial Hypertrophy (↑left Atrial pressure)*
- *Pulmonary Hypertension (Dilatation of pulmonary vessels)*
- *Right ventricular Hypertrophy (Secondary to pulmonary Hypertension)*
- *Right Atrial Hypertrophy (May be seen with severe M.S. secondary to Pulmonary Hypertension*

**Aortic Stenosis, Aortic Regurgitation and Mitral Regurgitation may all lead to Left Ventricular Hypertrophy**

Left Ventricular Hypertrophy may result from either pressure overload (e,g AS) or volume overload (MR, AR etc) of the left ventricle

**Left Ventricular Hypertrophy**

**Pressure Overload**

- Occurs when heart is forced to pump against increased resistance such as
  - Systemic ***Hypertension***$^{Q}$
  - Aortic ***stenosis***$^{Q}$
- These conditions cause ***systolic overload***$^{Q}$
- This causes ***concentric Hypertrophy***$^{Q}$ of left ventricle. (ventricular wall thickens in relation to ventricular cavity)

Systolic overload on ECG is characterized by :
- ↑QRS voltage
- Depressed ST segment
- Inverted T waves

} in left precordial Lead

**Volume Overload**

- Occurs when end diastolic wall stress is such as valvular regurgitation
- Aortic Regurgitation
- Mitral Regurgitation
- These conditions cause ***diastolic overload***$^{Q}$
- This causes ***Eccenteric hypertrophy***$^{Q}$ of Left ventricle (Ventricular wall thickness remains normal in relation to chamber dilatation

Diastolic overload on ECG is characterized by
- Tall Late 'R' waves in $V_5$ & $V_6$

**151. Answer is B (Serum Sodium) :** Harrison 18th/p 1906, 1907 *Harrison 16th/255, 1366; Harrison 17th/1447,1448; CMDT 2008/343; CMDT 2009/350*

***Congestive Cardiac failure is associated with Hyponatremia or Decreased Serum Sodium levels. – Hari. 16th / 255***

- **Heart failure is associated with Hyponatremia.** - *CMDT / Harrison*
  *Mechanism of hyponatremia is primary $Na^+$ gain exceeded by secondary water gain.*
  *In heart failure total body sodium is increased, yet effective circulating volume is sensed as inadequate by baroceptors. Increased ADH and Aldosterone results which causes retention of water and sodium. Secondary water gain exceeds primary sodium gain resulting in hyponatremia.*
- **Elevated serum urea levels may be seen.**
- *Biochemical studies in heart failure may show renal insufficiency. Renal functions tests also determine whether cardiac failure is associated with prerenal azotemia.*
- **Right atrial mean pressure is increased congestive heart failure.**
  In heart failure one or the other ventricle fails to discharge its contents or fails to fill normally.
  *As a result the pressure in the atrium and venous system behind (upstream) the failing ventricle rise.*
  - Harrison
- **In patients will heart failure the levels of circulating norepinephrine may be markedly elevated** *reflecting the increased activity of the adrenergic nervous system. - Harrison*

**152. Answer is C (Decreased after load):** Harrison 18th/p 1823 *Harrison 17th/1384; 'Textbook of Cardiovascular Medicine' by Topol 3rd/200*

***Hepatojugular reflux results from an increase in preload and afterload to the right atrium and ventricle (and not by a decrease in after load).***

*Hepatojugular reflux is a characteristic feature of Right ventricular failure. Tricuspid regurgitation and Pulmonic stenosis are both causes of right ventricular failure and may hence produce a positive hepatojugular reflux.*

**Hepatojugular Reflux**

Hepatojugular Reflux test is a helpful test in patients with suspected Right ventricular failure with a normal resting CVP (This test can be used to detect latent right heart failure)

Hepatojugular Reflux

With the patient in semirecumbant position (45° position) continuous pressure is applied with the palm of examiner over the abdomen / Liver for 10 seconds or more.

| In patients with compromised Right Ventricular Function | In patients with adequate Right ventricular Function |
|---|---|
| Abnormal Hepatojugular Reflux<br>Three is rapid elevation in JVP that remains persistently elevated by 4cm or more during the entire 10 seconds when pressure is maintained followed by a drop in pressure on release of compression. | Normal Hepatojugular Reflux<br>There may be a transient increase in JVP however the increase in JVP is not sustained for the entire '10' seconds when pressure is maintained and pressure rapidly returns to or near the baseline in less than 10 seconds even when pressure is still maintained. |

**Pathophysiology**

- During abdominal compression with increased abdominal pressure, there is an increased venous return to the right atrium and right ventricle (Increased preload)
  Concurrently there is an increase in right ventricular after load owing to upward movement of diaphragm which reduces the intrathoracic volume capacity.
- The normal functioning right ventricle handles this increase in preload and after load and systemic venous pressure remains normal.
- The dysfunctioning right ventricle however fails to accept this increase in preload and after load and hence systemic venous pressure remains persistently elevated.

Causes of Positive Hepatojugular Reflux

| Left Heart Failure | Right Heart Failure |
|---|---|
| The most common cause of Positive Hepatojugular Reflux in adults in Left Heart failure due to Dilated Cardiomyopathy (Constrictive Pericarditis and Restrictive cardiomyopathy may also cause a positive Hepatojugular Reflux). | Positive Hepatojugular Reflux may also be observed in patients with Right atrial or Right ventricular failure<br>• ***Tricuspid stenosis***<br>• ***Tricuspid Regurgitation***<br>• ***Pulmonary Hypertension***<br>• ***Right ventricular infarction*** |

**153. Answer is D (Decreased After-load):** *Harrisons 18th/1823, 1824, 1948; Textbook of Cardiovascular Medicine by Topal 3rd/200; Congestive Heart Failure by Greenberg (Lippincott) 2006 (3rd)/561*

***Positive Hepatojugular Reflux represents decreased compliance of the right ventricle and right atrium. This may result from an increase in preload and/or afterload to the right atrium and/or right ventricle.***
***Decrease in after-load does not cause a Positive Hepatojugular Reflux***

**154. Answer is A (Tricuspid Regurgitation (TR):** *Harrisons 18th/1948*

***Hepatomegaly (Enlarged liver) with systolic pulsations (of the liver) and ascitis are typically seen in Tricuspid Regurgitation.***

**Tricuspid Regurgutation**

The clinical features of Tricuspid Regurgitation result primarily from *systemic venous congestion and reduction in cardiac output.*

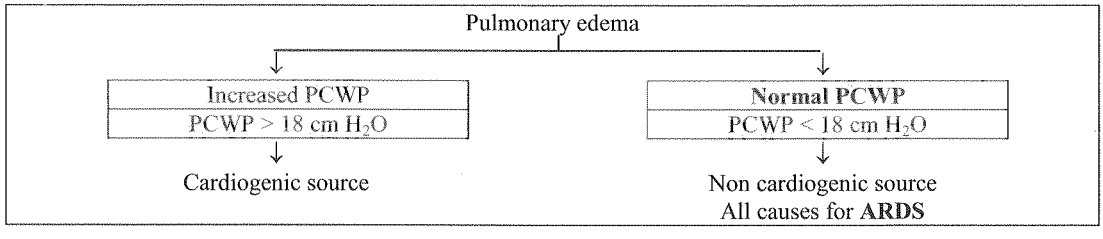
| Typical Physical Examination Findings in Tricuspid Regurgitation |
|---|
| • *Gross Fluid Retention*<br>  - *Significant Peripheral Edema*<br>  - ***Ascitis***<br>  - *Pleural Effusion*<br>• ***Hepatomegaly with a Pulsatile liver (Enlarged tender liver with systolic pulsations)***<br>• *Positive hepatojugular reflux*<br>• *Dilated Jugular veins with prominent 'v' waves and rapid 'y' decent*<br>• *Blowing Holosystolic murmur along lower left sternal margin that increases with inspiration*<br>• *Prominent RV Pulsations (Parasternal Heaves) over left parasternal region.* |

**155. Answer is A (Pulmonary Capillary Pressure):** *Hurst 12th/494*

***Pulmonary Capillary Wedge Pressure (PCWP) Closely approximates Left Atrial (LA)Pressure- Hurst 12th / 494.***

**156. Answer is A (Narcotic overdose):** Harrison 18th/p 281 *Harrison 16th/ 1592,204 Harrison 17th /224; API 7th/1240*

*Pulmonary edema with normal pulmonary capillary wedge pressure suggests a diagnosis of ARDS or non cardiogenic pulmonary edema. **Narcotic overdose is the only non cardiogenic cause for pulmonary edema (ARDS) amongst the options provided and hence the answer here.***




Causes of Pulmonary Edema with Normal Pulmonary Capillary Wedge pressure (PCWP=Normal)

| Direct Lung Injury | Indirect lung injury | Miscellaneous causes |
|---|---|---|
| • *Pneumonia*[Q]<br>• *Aspiration of gastric contents*<br>• *Pulmonary contusion*<br>• *Near drowning*[Q]<br>• *Toxic inhalation injury*[Q] | • *Sepsis*[Q]<br>• *Severe trauma:* [Q]<br>  - *Multiple bone fractures*<br>  - *Head trauma*<br>  - *Flail chest*<br>• *Burns*[Q]<br>• *Multiple transfusions*[Q]<br>• ***Drug overdose: eg Narcotic overdose***<br>• ***Pancreatitis***[Q]<br>• *Post-cardiopulmonary bypass*[Q] | • *Renal failure*[Q]<br>• *Liver failure*<br>• *Disseminated intravascular coagulation*[Q]<br>• *Ecclampsia*[Q]<br>• *Amniotic fluid emboli / Air emboli*[Q]<br>• *Hanging*<br>• *High altitude*[Q] |

**157. Answer is B (High Altitude):** Harrison 18th/p 2205 *Harrison's 16th/ 1592; Harrison 17th/ 1680; API 7th/ 1240*

*Pulmonary edema with normal pulmonary capillary wedge pressure suggests a diagnosis of ARDS or non cardiogenic pulmonary edema.*

***High altitude has been grouped as one of the miscellaneous causes for ARDS, reflecting pulmonary oedema with a normal PCWP - API 7th/ 1240***

**Some miscellaneous causes for ARDS**

- Renal failure
- Liver failure
- Disseminated intravascular coagulation
- Ecclampsia
- Amniotic fluid emboli / Air emboli
- Hanging
- High altitude

**158. Answer is D (Bilateral Renal Artery Stenosis)):** Repeat

***Bilateral Renal Artery Stenosis is not a cause for pulmonary edema with normal PCWP***
***High Altitude, narcotic overdose (Cocaine overdose),and cardiopulmonary bypass are all know causes for pulmonary edema with normal PCWP.***

**159. Answer is B (Drug induced cardiac toxicity):** *Harrison 16th / 584; 17th/ H-e 91, CMDT 2008 / 1418, 1675*

***Features of cardiac failure in a patient on doxorubicin suggests the possibility of Anthracycline induced cardiac toxity.Risk of Anthracyclinc induced cardiac toxicity is increased with concomitent radiation and cyclophosphamide. Cardiac failure after 6 months of chemotherapy with doxorubicin (anthracycline) and cyclophosphamide, is consistent with a diagnosis of drug induced cardiac toxity which is the single best answer of choice.***

**Anthracycline Induced Cardiac toxity**

- Most anthracyclines damage the heart muscle
- The problem is greater with doxorubicin because it has a major role and is used in repeated doses.
  - Change in cardiac dynamics occur in most patients by the time they have received 300mg/$m^2$ of doxorubicin.
  - Patient should not receive a total dose in excess of 450 ml/$m^2$
  - Toxicity may be irreversible at dosage level > 550 mg/$m^2$ (CHF)
    (About 5% of patient who receive > 550 mg/$m^2$ of doxorubicin will develop CHF).
- Anthracyline induced CHF is not readily reversible and mortality is as high as 50%.Thus prevention is the best approach - Harrison
- Risk of cardiotoxicity increase with radiation, cyclophosphamide – CMDT

**Anthracycline Antibiotics**

- Doxorubicin
- Daunomyocin
- Idarubicin

Mitoxantrone (Similar drug)

**160. Answer is a (BNP):** *Harrison18th/ 1907; 'Biochemical Markers in Congestive Heart Failure' Journal, Indian Academy of Clinical Medicine Vol. 11, No. 4 October-December, 2010*

***BNP is the most commonly used biomarker used in the diagnosis of Heart failure.***

*Levels of Brain Natriuretic Peptide (BNP), Endothelin -1 (ET-1), Atrial Natriuretic Peptide (ANP) and Adrenomedullin are all increased in Heart Failure. BNP has scored over others in prognostic, diagnostic, and therapeutic values and has also a found place in the guidelines for the diagnosis of congestive heart failure. Assays of BNP are commercially available and used clinically for screening and diagnosis of heart failure, to predict severity of condition and estimate prognosis.*

**Brain natriuretic peptide (BNP)** is a neuro-hormone released from ventricular myocytes in response to myocytes stress. It is released as a pro-hormone and cleaved into N-terminal (NT) pro-BNP and BNP. It causes vasodilation, diuresis, and natriuresis and decreases activity of Sympathetic Nervous System (SNS) and Renin-angiotensin-Aldosterone System (RAAS). Both BNP and NT-pro-BNP have prognostic value in heart failure. Those with higher values on admission do worse and those whose values decrease after treatment fare better. Out of BNP and NT-pro - BNP, NT-pro-BNP is superior to BNP in predicting hospitalisation and death in heart failure.

| **BNP /NT-pro-BNP Assays:** |
|---|
| • It helps in screening patients at risk of development of heart failure (Diabetics and asymptomatic coronary artery disease)<br>• It helps in deciding whether heart failure is the cause of dyspnoea in the emergency department (A very low BNP or NT-pro-BNP helps exclude a cardiac cause of dyspnoea)<br>• It has prognostic value in heart failure (Those with higher values on admission do worse and those whose values decrease after treatment fare better) Out of BNP and NT-pro-BNP, NT-pro-BNP is superior to BNP in predicting hospitalisation and death in heart failure. |

Note: At present serial measurement of BNP are not recommended as a guide for Heart Failure Therapy

| **Neurohormonal Markers raised in Heart Failure** |
|---|
| • *Atrial Natriuretic Peptide (ANP)*<br>• *Brain Natriuretic Peptide (BNP)*<br>• *Endothelin-1 (ET-1)*<br>• *Adrenomedullin* |

*Levels of Endothelin -1 (ET-1) , Atrial Natriuretic Peptide (ANP) and Adrenomedullin are also increased in Heart Failure*
***BNP has scored over others in prognostic, diagnostic, and therapeutic values and has also a found place in the guidelines for the diagnosis of congestive heart failure***

**161. Answer is C (Endothelin-1):** *Essentials of Pathophysiology: Concepts of Altered Health States (Lippincott Williams & Wilkins, 2011)/ 493*

***Endothelin-1 (ET-1) levels have been found to correlate best with pulmonary vascular resistance in patients with Heart Failure.*** *Heart failure is associated with increase in plasma levels of Endothelin-1 (ET-1). Endothelin-1 (ET-1) is amongst the most potent endogenous vasoconstrictors. The pulmonary circulation is the primary source of expression of this neurohormone and ET-1 Levels have been found to correlate with pulmonary vascular resistance.*

*'Plasma ET-1 Levels correlate directly with pulmonary vascular resistance and it is thought that this peptide may play a role in mediating pulmonary hypertension in persons with heart failure' - Essentials of Pathophysiology (2011)/ 493*

**162. Answer is a (BNP):** *Harrison18th/ 1907; Essentials of Pathophysiology: Concepts of Altered Health States (Lippincott Williams & Wilkins, 2011)/ 493; http://medind.nic.in/jac/t10/i4/jact10i4p282.pdf*

***Brain natriuretic peptide (BNP) is a neurohormone primarily released from ventricular myocytes in response to myocytes stress.*** *(Misnomer: Named Brain-NP because it was originally found in extracts of porcine brain)*

| | |
|---|---|
| Atrial Natriuretic Peptide (ANP) | ***Released from atrial myocytes in response to atrial stretch, pressure or fluid overload*** |
| Brain Natriuretic Peptide (BNP) | ***Released from ventricular myocytes in response to myocyte stress from increased ventricular pressure or volume overload***<br>*(Misnomer: Named Brain-NP because it was originally found in extracts of porcine brain)* |
| Endothelins | ***Released from endothelial cells*** |

**163. Answer is A (Digoxin):** *Harrison 18th/2236, 2237; Kumar & Clarke 7th/343; European Society of Cardiology Guidelines; Modern Management of cardiogenic Pulmonary Edema (Emergency Medicine Clinics of North America); Americal College of Cardiology/Americal Heart Practice Guidelines*

***Digoxin has no definitive role in the management of Acute Pulmonary Edema***

*'Digitalis is not the initial drug of choice for management of patients with acute severe pulmonary edema (severe heart failure) because of its mild inotropic effect and because of the delay in time to peak action. It should not be used in the management of acute cases, in the absence of atrial arrhythmias as its use may complicate an already difficult management problem. Digoxin is only recommended if the patient is in atrial fibrillation and this is contributing to the cardiac failure – 'Circulation' Journal of American Heart Association*

*'Digoxin is not recommended in acute pulmonary edema unless there is associated rapid atrial fibrillation. Rapid atrial fibrillation in this situation is better treated with urgent cardioversion'* – *'Coronary care manual' by Thompson (Elsevier) 2nd/508*

*'Digoxin has no definitive role in the management of acute congestive heart failure (acute pulmonary edema)'*
*– Clinical Emergency Medicine (Cambridge University Press) 2005/499*

*'Once a mainstay of treatment because of their positive inotropic action digitalis glycosides are rarely used at present. However they may be useful for control of ventricular rate in patient with rapid atrial fibrillation or flutter with LV dysfunction' – Harrison 18th/2237*

Initial Management of Acute Pulmonary Edema (Acute Heart Failure)

- *Oxygentation* with face mask or ***Positive Pressure Ventilation (Non invasive)***
- ***Vasodilatation by Nitrates (or Nitroprusside)***
- ***Diuretic therapy by Furosemide (or other loop diuretics)***
- *Morphine* for relief of physical psychological stress and to improve haemodynamics.

*Inotropes should be used based on clinical and haemodynamic parameters of the patient who does not respond to initial treatment.*

**Acute Pulmonary Edema**

| Oxygen and Ventilatory Support | Morphine | Vasodilators | Diuretics | Inotropic Agents |
|---|---|---|---|---|
| • **Supplemental oxygen** The maintenance of SaO2 within normal limits (95-98%) is important to maximize oxygen delivery to tissues<br>• **Non invasive ventilation** (without endotrachial intubation)<br>*CPAP or Non invasive positive Pressure Ventilation (NIPPV)*<br>*The use of CPAP and NIPPV in Acute Cardiogenic Pulmonary Edema is associated with a significant reduction in the need of tracheal intubation and mechanical ventilation.* | *Morphine* diminishes anxiety and decreases sympathetic outflow, thereby reducing both venous and arterial vasoconstriction resulting in decreases in ventricular preload and after load.<br>• *Morphine is recommended for the treatment of Acute severe pulmonary edema especially if associated with restlessness and dyspnea* (effectively ameliorates symptoms) | *Vasodilators* are indicated in most patients with acute pulmonary edema (AHF) as first line therapy if associated with adequate blood pressure and signs of congestion with low diuresis to open the peripheral circulation and to lower preload.<br>• Nitrates (sublingual/Intravenous) (Agent of choice)<br>• Nitroprusside (Associated Hypertensive Crisis)<br>• Nesiritide | *Diuretics* are recommended for initial management of acute severe pulmonary edema especially in the presence of symptoms secondary to fluid retension (Reduce Alveolar Edema)<br>• Intravenous administration of Loop Diuretics (Furosemide, Bumetonide or Torasemide) is the preferred choice due to their strong and brisk diuretics effect. | *Inotropic agents* are indicated in the management of Acute pulmonary edema in the presence of peripheral hypoperfusion (hypotension/reduced renal function) with or without congestion or pulmonary edema refractory to diuretics and vasodilators at optimal doses.<br>• Dobutamine/Dopamine<br>• Phosphodiesterase Inhibitors (Milrinone / Enoximone)<br>• Levosimenden<br>• Norepinephrine/ Epinephrine |

***Digoxin is not recommended as on inotrope for the management of Acute pulmonary Edema*** *because of its mild inotropic effect and delay in time to peak action (slow action). Digoxin may be selectively considered for patients with Atrial Fibrillation where AF is contributing to cardiac failure / pulmonary edema.*

**164. Answer is D (Trimetazidine):** *Harrison 18th/1907-12; KDT 6th/534, 535, 502; Harrisons 17th/ 1449, 1450, 1451, 1452*

***Trimetazidine is not used in the management of congestive heart failure.***

**Trimetazidine** *is a novel anti-ischemic agent used for the treatment of coronary conditions like angina. Although it's exact mechanism of action is not known, it is believed to act by improving cellular tolerance to ischemia unlike other conventional antianginal agents.*

**Spironoloactone, Nitrates and Nesritide may all be used in the managed of congestive Heart Failure**

- Nestritide and nitrates are vasodilatory that help CHF by lowering left ventricular filling pressures (by decreasing preload)
- Spironolactone is an aldosterone antagonist that helps in CHF by antagonizone tha effects of aldosterone.

**Drugs Used in Heart Failure**

| Drugs which help in relieving congestive / low output symptoms and restoring cardiac performance | Drugs which help in arresting / reversing disease progression and prolonging survival |
|---|---|
| • **Diuretics**<br>- *Furosemide Torsemide / Bumetanide / Hydrochlorthiaizide / Metazolone*<br>• **Vasodilators**<br>- **Nitrates**<br>- Nisoprusside<br>- **Nesiritide**<br>• **Inotropes**<br>- *Digoxin*<br>- *Dopamine / Dobutamine*<br>- *Mitrinone*<br>- *Levasimendan*<br>• **Vasoconstrictors** (to maintain blood pressure)<br>- *Dopamine for Hypotension*<br>- *Epinephrine / Phenylephrine*<br>- *Vasopressin* | • **ACE Inhibitors**<br>- *Captopril / Enalapril / Lisinopril / Ramipril etc*<br>• **Angiotension Receptor Blockers**<br>- *Losartan / Valsartan / Irbesartan etc*<br>• **Beta Blockers**<br>- *Carvedilol / Bisoprolol / Metoprolol*<br>• **Aldosterone Antagonist**<br>- ***Spironolactone*** |

**165. Answer is A (They should be initiated at the effective doses):** Harrison 18th/p 1909 *Harrison's 17th/1450, 51; KDT 6th/505, 506; Goodman & Gillman's Manual of Pharmacology (2007)/570*

***Beta blocker should be initiated at lower than effective doses in CHF***

**Beta blockers should be initiated at lower than effective doses in CHF and be**

*'Beta blockers **should be initiated at low doses** followed by gradual increments in the dose if lower doses have been well tolerated. The dose of beta blockers should be increased until the doses used are similar to those that have been reported **effective** in clinical trials. The titration of beta blockers should proceed no more rapidly than at 2 week intervals because the initiation and / or increased dosing of these agents may lead to worsening fluid retention' – Harrison's 17th/1450*

**Special precaution should be taken in NYHA class III & IV**

*'Although data suggests that patients with NYHA class IIIB and IV CHF may tolerate beta blockers and benefit from their use, this group of patients should be approached with considerable caution'*

*–Goodman & Gillman's Manual of Pharmacology (2007)/570*

**Carvedilol and Metoprolol are the preferred beta blockers in CHF**

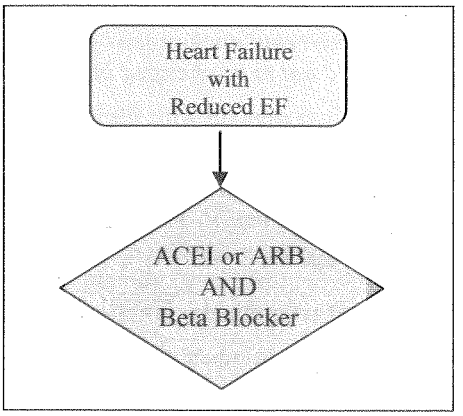
*'Non selective third generation beta blockers (Bucindolol, **Carvedilol**) as well a the Beta-1 selective agent (**Metoprolol**) are generally well tolerated by patients with CHF'.*

*- 'Current Diagnosis & Treatment in Cardiology' 3rd/217*

**166. Answer is A (ACE-I + Beta Blocker):** *Clinical Cardiology : Current Practice Guidelines*

***The initial treatment of choice for all patients with Heart Failure and a reduced ejection fraction of < 40 percent (Systolic Heart Failure) is a combination of ACE-Inhibitor and Beta Blocker.***

| Recommendations for treatment of Heart Failure with Reduced Ejection Fraction (< 40 percent) |
|---|
| • Prescribe an ACE inhibitor together with a β-blocker for all heart failure patients with Left Ventricular Ejection Fraction (LVEF) of < 40% and symptoms of heart failure unless a specific contraindication exists.<br>• Use one of the three beta blockers that have proven to reduce mortality in all stable patients (Carvedilol, Bisoprolol and/or Metoprolol).<br>• Use angiotensin receptor blockers (ARBs) in patients who cannot tolerate ACE inhibition |




**167. Answer is C (Calcium Channel Blockers):** *The Cleveland Clinic Cardiology Board Review ; Clinical Cardiology : Current Practice Guidelines*

***There is no survival advantage in using calcium channel blockers (CCBs) in Heart Failure. Drugs hat have shown to reduce mortality from CHF should be used and maximized*** before using CCBs for the treatment of angina pectoris or hypertension associated with Heart Failure.

| Medications that have shown to lower mortality in CHF |
|---|
| • ACE inhibitors and ARBs<br>• Beta-blockers<br>• Aldosterone antagonists (spironolactone)<br>• Hydralazine, plus nitrate |

**168. Answer is D (Digoxin):** *CMDT 2003/384, 385, 386;* Harrison 18th/p 1906, 1908, 1909 *Harrison 16th/1375; Harrison 17th/1448-1451; CMDT 2009/354*

*'Digitalis does not improve survival in patients with heart failure and sinus rhythm.' – Harrison 16th/ 1375*

***It reduces symptoms of heart failure and need for hospitalization. ACE inhibitors (Corvedilol and enalapril) and Betablockers (Metaprolol) prolong life.***

**'ACE inhibitors** improve symptoms and prolong life' – *Oxford handbook 5th/ 122*
ACE inhibitors – Harrison 16th

| Patients with LV dysfunction without HF | Patients with HF/ After Acute MI / with vascular disease |
|---|---|
| Prevents or retards development of H.F. | • Reduces symptoms<br>• Enhances exercise performance<br>• *Reduces long term mortality* |

**Beta blockers :** 'Recent randomized trials show that β blockers decrease mortality in heart failure'-*Oxford handbook 5th/ 122*

| Administration of gradually escalating doses of β-blockers has shown to: (Harrison) |
|---|
| • Improve symptoms of HF<br>• *Reduce all – cause death:*<br>- Cardiovascular death<br>- Sudden death<br>- Pump failure death<br>• Reduce rehospitalization for HF |

**169. Answer is C (Actively metabolized in Liver):** *KDT 5th/ 461, 462*

***Digoxin is excreted unchanged by the Kidney***, mainly by Glomerular filtration. ***It is not metabolized by liver. Dose of digoxin need not to be changed in Liver failure.***

**Do not confuse digoxin with digitoxin :**

- *The* most *lipid soluble cardiac glycoside is = Digitoxin* Q
- *The* most *rapidly absorbed oral glycoside is = Digitoxin* Q
- Digitoxin *is primarily metabolized by the liver* Q
- *Dose of digitoxin needs to be reduced in liver failure.* Q

**170. Answer is D (Hepatic dysfunction):** *KDT 4th/ 498, KDT 5th/ 463*

**Digoxin toxicity** is enhanced by *renal failure* as it is excreted through kidneys where as **digitoxin toxicity** is enhanced by liver failure because it is eliminated by hepatic metabolism. Hepatic dysfunction does not affect digoxin elemination.

**Reduced tolerance to digoxin may be seen in :**

- Advanced age Q
- Acute myocardial infarction Q / ischaemia / hypoxemia
- Magnesium depletion Q
- Hypercalcemia Q
- Hypothyroidism Q
- Renal insufficiency Q
- Electrical cardioversion.

**The administration of following drugs raises the serum concentration of digoxin :**
*(by reducing both the renal and nonrenal elimination of digoxin and by reducing its volume of distribution)*

- *Quinidine* Q
- *Verapamil* Q
- *Amiodarone* Q
- *Propafenone* Q

**171. Answer is A (Hypocalcemia):** *KDT 4th/ 449, 448, KDT 5th/ 463, 464; Harrison 14th/1295, 16th/ 1375; CMDT 2008/347*

***Calcium synergizes with digitalis and precipitates its toxicity***. *Thus digitalis toxicity is associated with hypercalcemia and not hypocalcemia*

***Also Remember:***

- ***Digitalis does not cause Hypokalemia*** Q ***but Hypokalemia enhances digitalis toxicity*** Q
  - Digitalis toxicity causes Hyperkalemia Q - *Harrisons*
  - Hypokalemia enhances digitalis toxicity (by increasing its binding to Na+/K+ ATPase Q
- ***Both Hyperthyroidism and Hypothyroidism enhance digitalis toxicity***
  - Thyrotoxicosis : patients are more prone to develop digitalis arrhythmia. Q
  - Myxoedema : enhances responsiveness. These patients eliminate digoxin more slowly. Q
- ***Magnesium depletion (hypomagnesimia) may reduce tolerance to digitalis*** Q *- Harrison 16th / 1375*

**172. Answer is D (Hemodialysis):** *Harrison 15th/ 1327; Harrison 16th/ 1375; CMDT 2008/347; KDT; CMDT 2009/354*

***Hemodialysis has no role in treatment of digoxin overdose.***

**Management of digitalis overdose includes:**

- Withdrawl of drug Q
- *Potassium*Q: administer *cautiously and by oral route* whenever possible if hypokalemia is present. Potassium must not be employed in the presence of A-V block or hyperkalemia
- *Phenyloin/β blocker or Lidocaine* Q : Lidocaine is effective in treatment of digitalis induced ventricular tachyarrhythmias.
- *Cardiac pacemaker* : may be required in digitalis induced A-V block

- *Electrical conversion* : may be life saving in digitalis induced ventricular fibrillation
- *FAB fragments/digitalis antibodies* [Q] : are potentially life saving in severe intoxication.

***Hemodialysis is not useful in poisonings due to:***

- *Digoxin* [Q]
- *Kerosene* [Q]
- *Benzodiazepines* [Q]
- *Organophosphates* [Q]

**173. Answer is D (Haemodialysis):** *Harrisons 16th/1375, KDT 6th/498,499; Refer previous question*

***Hemodialysis is not useful in digitalis poisoning.***

**174. Answer is B (Prominent lower lobe vessels):** Harrison 18th/p 1914 *Harrison 17th/ 1447, 1454; Read text below*

***Congestive cardiac failure or corpulmonale are associated with prominence of upper lobe vessels and not lower lobe vessels.***

***Features of Congestive Cardiac Failure(CCF / CHF) include :***

1. ***Enlarged cardiac silhouette / Cardiac shadow on chest X-ray*** [Q]
2. Ground glass appearance of pulmonary edema [Q]
3. ***'Kerley B' lines*** [Q]
4. ***Prominence of upper lobe blood vessels*** [Q] *(not lower lobe veins)*
5. *Pleural effusion, usually bilateral* [Q]

***'Kerley B' lines'**, also known as **'Septal lines'**, represent dilated lymphatics and distended interlobular septa. They occur **most commonly in pulmonary edema as a result of chronic pulmonary venous hypertension (in CCF).***

*Kerley 'A' lines stand for Apex, 'B' for Base, and 'C' for Central region.*

***B lines are most commonly seen*** [Q]. ***Infact they have a relation with left atrial pressure*** [Q] *: They are invariably present if LA pressure goes above 20 mmHg.* [Q]

## Valvular Heart Diseases

### Mitral Stenosis

**175. Answer is C (4-6 $cm^2$):** *Braunwald 6th/378,1643,1673*

***The normal area of mitral valve is 4-6 $cm^2$.***

| Mitral Valve & pathology | Area |
|---|---|
| *Normal Mitral Valve* | *4-6 $cm^2$* [Q] |
| *Mild Mitral Valve* | *< 2 $cm^2$* |
| *Severe Mitral Stenosis* | *< 1.3 $cm^2$* [Q] |
| *Critical Mitral Stenosis* | *< 1 $cm^2$* [Q] |
| *Aortic Valve & pathology* | *Area* |
| *Normal Aortic Valve* | *2.6 – 3.5 $cm^2$* [Q] |
| *Mild Aortic Stenosis* | *1.5 – 2 $cm^2$* |
| *Moderate Aortic Stenosis* | *1 – 1.5 $cm^2$* |
| *Severe Aortic Stenosis* | *< 0.8$cm^2$* |

**176. Answer is A (Right ventricular hypertrophy):** Harrison 18th/p 1931 *Harrison 15th/1343, Harrison 16th/ 1390; Harrison 17th/ 1467*

***Mitral stenosis is associated with right ventricular hypertrophy.***

*Left ventricular diastolic pressure is normal in isolated MS – Harrison 16th/ 1390*

**Mitral stenosis : Features**

- left atrial pressure is increased
- pulmonary arterial pressure is increased
- Increased right ventricular after load impedes the emptying of this chamber and Right ventricular end diastolic pressure and volume increase.
- Right ventricular hypertrophy occurs.

**177. Answer is A (Mitral Stenosis):** *Harrison 17th /1467*

***Mid diastolic murmur with with presystolic accentuation is typically seen in mitral stenosis.***

*'Mitral stenosis is associated with a low pitched rumbling diastolic murmur heard best at the apex. The murmur typically peaks during middiastole and again immediately before the first heart sound* ***(Pre-systolic accentuation)****'*
*- Evidence Based physical diagnosis (Elsevier) 2012/397*

*'Mitral stenosis is associated with a low pitched rumbling diastolic murmur heard best at the apex with the patient in lateral decubitus position. In patients with sinus rhythm, the murmur often reappears or becomes louder during atrial systole* ***(presystolic accentuation)'*** *- Harrison*

**Mitral stenosis : Review**

**Mitral stenosis**

**Auscultatory findings**

- $S_1$ : *accentuated.*
- $S_2$ : *Normally split $S_2$ with accentuated $P_2$*[Q]
- **Murmur :** *Low pitched*[Q]*, rumbling*[Q] *diastolic murmur*[Q] *with 'Pre-systolic accentuation' heard best at the apex in left lateral recumbent position*[Q].
- **Opening snap:** *brief, high pitched*[Q]*, early diastolic*[Q] *sound, best heard at the lower left sternal border*[Q].

**X Ray findings**

- *Straightening of the left border of cardiac silhouette*[Q]
- *Prominence of main pulmonary artery*[Q]
- *Dilation of upper lobe pulmonary veins*[Q]
- *Kerley B lines*[Q]
- *Backward displacement of the esophagus*[Q]

**178. Answer is C (Opening snap delayed from S2):** *Harrison 17th /1467*

***The interval between opening snap and S2 is shortened (reduced) as severity of mitral stenosis increases.***

*'The opening snap generally follows the sound of Aortic valve closure (A2, S2) by 0.5 – 0.12 seconds. The time interval between S2 and OS varies inversely with the severity of MS'- Harrison 18th/1930*

**Features suggesting severe M.S.**

- *Proximity of S2-OS gap* [Q]
- *Longer Duration of mid –diastolic murmur* [Q]

**Atrial Fibrillation may be seen in severe Mitral stenosis**

Mitral stenosis and mitral regurgitation are common causes of Left atrial enlargement which predisposes to AF. The probability of AF increases as severily of MS increases.

*'The irregularly irregular pulse of AF usually means severe mitral stenosis except in elderly patients when AF can occur with mild mitral stenosis' - 'Clinical Methods in cardiology' by Raju (Orient Blackswan) 2003/201*

**Pulsatile liver may be seen in severe Mitral Stenosis**

*Enlarged Pulsatile Liver is essentially a feature of Tricuspid Regurgitation*[Q]*. Patients with severe MS have pulmonary hypertension that may cause Tricuspid Regurgitation and result in a pulsatile liver.*
*-'Specialist Training in Cardiology' by Rao (Elsvier, India) 2007/339*

**179. Answer is B (Length of murmur):** *Harrison 18th/p 1930, 1931; Harrison 14th/ 1313, Harrison 15th/ 1344-45, Harrison 16th/ 1391; 17th/ 1467*

*'The duration of murmur correlates with the severity of stenosis - Harrison*

**Features suggesting severe MS are :**

1. *Proximity of S2 - O.S. gap* [Q]*, and*
2. *Longer duration of mid-diastolic murmur* [Q]

**180. Answer is B and C ($S_2$ – OS gap and Prolonged Diastolic murmur):** Harrison 18th/p 1930, 1931 *Harrisons 17th/1467; Harrisons 16th/1391*

***The severity of mitral stenosis may be clinically judged by the gap between the opening snap (OS) and the aortic component of second heart sound ($S_2$) and by the duration of diastolic murmur.***

**Features suggesting severe M.S.**

- *Proximity of S2-OS gap* Q
- *Longer Duration of mid –diastolic murmur* Q

**181. Answer is D (Short A2 –OS interval)**

***In Mitral Stenosis, the interval between the Aortic Closure Sound (A2) and the Opening nap (OS) is inversely related to the Mean Left Atrial Pressure (PCWP)***

PCWP measures the left atrial pressure. In Mitral Stenosis the interval between the aortic component of the second heart sound (A2)and the opening snap (OS) of the mitral valve typically shortens, with smaller mitral valve orfice size and rising Left Atrial Pressure (increasing severity of stenosis). Decreasd A2-OS interval is indicative of Elevated Left Atrial Pressure (Increased PCWP) from smaller mitral valve orfice (Increase in severity of stenosis)

*The interval between the Aortic Closure Sound (A2) and the Opening nap (OS) is inversely related to the Mean Left Atrial Pressure (PCWP)*

**182. Answer is B (Left Atrium):** *Radiology for Undergraduates and General Practitioners (Jaypee) / 65; 101 Chest X-Ray Solutions (Jaypee) / 189; Grainger's 4th/ 684; http://circ.ahajournals.org/content/123/24/2897.full*

***Double Density sign in Mitral Stenosis is a sign of enlargement of Left Atrium***

***Double-density sign in Mitral Stenosis is seen on frontal chest radiograph as a result of left atrial enlargement towards the right side.*** It occurs when the right side of the left atrium pushes behind the right cardiac shadow and if large enough can actually reach beyond the border of the right atrium (this is known as atrial escape). ***With progressive left atrial enlargement toward the right side, the right heart border shows a double density comprising a radio-denser right atrial shadow superimposed within a fainter left atrial shadow that touches the diaphragm.***

## Mitral Regurgitation

**183. Answer is C (Left Ventricular $S_3$) :** *' The Art and Science of Cardiac Physical Examination' by Ranganathan & Value 1st/243*

***The severity of Mitral Regurgitation may be judged clinically by the presence of left ventricular dilatation and the presence of third heart sound (Left Ventricular $S_3$). These features indicate a more severe disease***

*'A third heart sound ($S_3$) in chronic mitral regurgitation is usually indicative of severe regurgitation'*

Severity of Mitral Regurgitation : Features indicating increased severity:

- ***Presence of Left ventricular $S_3$ or an inflow rumble at the apex***
- *Harsh Decrescendo murmur with lot of low and medium frequencies*
- *Wide split $S_2$ due to early $A_2$ (not caused by $P_2$ delay) in presence of MR*

**Severity of Mitral Regurgitation:**

1. If the murmur is harsher and has a lot of low and medium frequencies. It usually indicates a lot of flow and therefore will imply significant regurgitation.
   A harsh decrescendo mitral regurgitation murmur is usually indicative of severe regurgitation because the decrscendo effect is caused by early buildup of a very high v wave pressure in the left atrium resulting from a severe degree of regurgitation. Thus decreasing the gradient in late systole
   (If the murmur, on the other hand, is all pure high frequency and confined only to late systole. Then it must indicate a high pressure difference between the left ventricle and the left atrium and therefore only mild regurgitation).
2. When the mitral regurgitation is severe, the volume overload on the left ventricle will be high, resulting in an enlarged left ventricle. This may be reflected in a displaced hyperdynamic wide –area left ventricular apical impulse. In addition, the hyperdynamic left ventricle will have rapid ejection. This will make the A2 occur early. Resulting in a wide-split S2. Thus, a wide –split S2 in the presence of mitral regurgitation is a sign of severe regurgitation if the wide split is not caused by P2 delay.
3. In addition, severe regurgitation because of the volume load effect will have a torrential inflow through the mitral valve during diastole. This will set up the necessary conditions for the production of an S3 or a mid –diastolic inflow rumble. The presence of an S3 or an inflow rumble at the apex will, therefore, be a sign of significant mitral regurgitation as well.

**Note**

*Loudness and duration of Mitral regurgitation murmur does not always correlate with the severity of the regurgitation*

**184. Answer is None or D (Intensity of systolic murmur across mitral valve):** *References with individual options; O.P. Ghai Pediatrics 5th/ 279, 280, 281;* Harrison 18th/p 1935 *Harrison 17th/ 1470*

***Intensity of Mitral regurgitation murmur does not always correlate with the severity of the regurgitation.***

*Probably all features mentioned in the option may suggest severe MR. The presence of systolic mumur of at least grade III/VI suggests severe MR, but no where does any text suggest that intensity of this murmur shall increase with the severity of MR. Therefore this may probably be the single best answer of exclusion.*

**Features suggesting severe MR:**

| | |
|---|---|
| • LV enlargement: | 'The degree of LV enlargement usually reflects the severity of regurgitation' – *CMDT 2005/ 233* |
| • Wide split of $S_2$: | 'In patients with severe MR, the aortic valve may close prematurely resulting in wide splitting of $S_2$' – *Harrison 16th/ 1394* |
| • Third heart sound '$S_3$': | 'A third heart sound is an important auscultatory feature of severe MR' – *Harrison 16th/ 1394* |
| • Fourth heart sound '$S_4$': | A fourth heart sound is often audible in patients with acute severe MR of recent onset who are in sinus rhythm. |
| • Systolic murmur: | 'A systolic murmur of at least grade III/VI intensity is the most characteristic auscultatory finding in severe MR' – *Harrison 16th/ 1394* |
| • Diastolic murmur: | 'With severe mitral regurgitation, a delayed diastolic mitral murmur starting with the third heart sound is audible' – ***Ghai 6th/ 381*** The delayed diastolic murmur is secondary to a large flow across the mitral valve during diastole. |
| • Pulmonary hypertension: | Presence of features of pulmonary arterial hypertension in a patient having pure mitral regurgitations suggests, severe MR, acute MR or a failing myocardium' – *Ghai 5th/ 380* |

*From the above texts it is clear that all features mentioned as options may suggest severe MR. However if we focus on the option of systolic murmur which does not state merely the 'presence of a systolic murmur' but the 'intensity of systolic murmur across the mitral valve' as a reflection of the severity of MR. We may have our doubts. The presence of systolic murmur of at least grade III/VI suggests severe MR, but nowhere does any text suggest that intensity of murmur shall increase with the severity of MR..*

**185. Answer is A (Mitral valve repair or replacement) :** Harrison 18th/p 1936 *Harrisons 16th/ 139538.5; Harrison 17th/ 1471*

***"Surgical treatment of severe MR should be considered even in asymptomatic patients or those with mild symptoms whose LV dysfunction is progressive with LV ejection fraction declining below 60%"*** *- Harrisons*

**Indications of surgical management :**

| Symptomatic patient | Asymptomatic patient |
|---|---|
| Patients with severe MR whose limitations do not allow full time employment or the performance of normal household activities despite optimum medical management. | Asymptomatic patients when LV dysfunction is progressive<br>*LVEF* — Declining below 60%<br>*Endosystolic cavity dimension on Echo* — Rising above 45mm |

## Mitral Valve Prolapse (MVP)

**186. Answer is A (Myxomatous degeneration):** Harrison 18th/p 1937 *Harrison's 17th/1472*

***Presence of midsystolic click in an asymptomatic female suggests a diagnosis of Mitral Valve Prolapse (MVP). MVP is associated with myxomatous degeneration of the mitral valves.***

*Ruptured chordae tendinae may be seen in MVP but these patients are usually symptomatic with significant Regurgitation (MR).*

**Mitral Valve Prolapse Review**

- Also known as *'Barlow's syndrome'* [Q] *or 'Billowing mitral valve'* [Q] *or 'Floppy valve syndrome'* [Q].
- It is most common in *females* [Q]
  Most commonly seen in young adults (15 to 50 years)
  (MVP may be seen in older individuals > 50 yrs. When seen in older individuals most patients are males and MR is more common and severe and requires surgical treatment)
- Inheritance in familial cases is *autosomal dominant* [Q].
- Clinical course is usually benign
  - Patients are *usually asymptomatic* [Q]
  - Patients may present with *non specific chest pain, dyspnea, fatigue and palpitations.* [Q]
- Auscultatory findings are characteristic and most important :
  - Characteristic *mid systolic* [Q] or late systolic *non ejection* [Q] *clicks* [Q] which may be *multiple* [Q]
  - Late systolic ejection murmur (Often but not always)
  - Accentuation of findings by *Valsalva and standing.* [Q]
  - Diminished by *squatting and isometric exercises.* [Q]
- Diagnosis :
  - *Investigation of choice is echocardiography.* [Q]
  - *ECG in most cases is normal.* [Q]
- Pathological Findings:
  - ***Myxomatous degeneration of mitral valve (less commonly in tricuspid and aortic valves)***
  - Elongated, Redudant or Ruptured chordae tendinae
    (patients with ruptured chordae tendinae are usually symptomatic with significant regurgitation – MR)
  - Dysfunction and ischaemia of papillary muscles
  - Progressive dilatation and calcification of mitral valve annulus
- Complications :
  - *M.R* [Q].
  - *Arrythmias* [Q]
  - *Sudden death* [Q]
  - *Transient ischemic attack* [Q]
  - *Infective endocarditis* [Q]

**187. Answer is B (Most patients are symptomatic):** Harrison 18th/p 1937 *Harrisons 17th/1472; Harrisons 16th/1395,1396*

*Most patients are asymptomatic and remain so for their entire lives- Harrisons 17th/1972*

**188. Answer is B (Mostly Symptomatic):** Harrison 18th/p 1937 *Harrisons 17th/1472: Harrisons 16th/1395,1396*

*Most patients are asymptamatic and remain so for their entire lives)-Harrisons 17th/1472*

**189. Answer is B (Majority of the case present with features of mitral regurgitation):** Harrison 18th/p 1937 *Harrison 16th/1395, 2330; CMDT 2006/330, 331*

*Majority of patients with MVP are asymptomatic but may present with non specific chest pain, dyspnea, fatigue or palpitation. MVP has distinct auscultatory presentation in the form of mid or late non ejection systolic clicks. Mitral regurgitation is seen only as a complication of MVP resulting from rupture of chordae tendinae or failure of papillary muscles.* ***Thus although features of mitral regurgitation may be associated in cases of MVP, these are definitely not the presenting features in the majority.***

- ***Valve leaflets show myxomatous degeneration***
  'In most patients with MVP, however **myxomatous degeneration** is confined to the mitral or less commonly the tricuspid or aortic valves without other clinical or pathologic manifestations of disease' – Harrison 16th/1395
- ***Autosomal dominant inheritance***
  *There is an increased familial incidence suggesting an* **autosomal dominant form of inheritance'**– Harrison 16th/1395
- ***The disease is one of the common cardiovascular system manifestations of Marfans syndrome***
  *'**Cardiovascular abnormalities are the major source of morbidity and mortality** (in patients with Marfan's syndrome). Mitral valve prolapse develops early in life and in one quarter of patients progresses to mitral valve regurgitation of increasing severity' – Harrison 16th/2330*

**190. Answer is C (Echocardiography):** Harrison 18th/p 1937 *Harrison 14th/ 1317, Harrison 15th/ 1348; 16th/ 1395, 1396; Harrison 17th/ 1472*

***The history suggests the diagnosis of 'Mitral valve prolapse'(MVP).***
***Investigation of choice for MVP is Echocardiography.***

**191. Answer is A (Echocardiography):** Harrison 18th/p 1937 *Harrison 16th/ 1396; Harrison 17th/ 1472*

***The investigation of choice in MVP is echocardiography.***

Two dimensional echocardiography is particularly effective in identifying the abnormal position and prolapse of mitral valve leaflets.

## Aortic Stenosis

**192. Answer is B (Aortic stenosis):** Harrison 18th/p 1939 *Harrison 14th/ 1318, Harrison 16th/ 1397; Harrison 17th/ 1472*

***Angina pectoris and Syncope are characteristic features of Aortic stenosis.***

**Aortic stenosis is characterized by the following cardinal features:**
- ***Dyspnea*** Q
- ***Angina pectoris*** Q
- *Exertional syncope* Q
- *Sudden Death*

**193. Answer is C (Aortic stenosis):** *Harrison 18th/p 1939 Harrisons 16th/1397; 17th/ 1473; CMDT 2006/333; CMDT 2009/302; OHCM 6th/136*

*'Angina pectoris, Exertional syncope, and dyspnea (LV failure) represent the charactristic clinical triad of Aortic stenosis.' - Harrison 16th/1397*

***'Patients present with LV failure, angina pectoris or syncope** all occurring with exertion.' - CMDT 2006/ 333*

**Symptoms of Aortic Stenosis**

| Dyspnea Q | Angina Pectoris Q | Syncope (Exertional) Q |
|---|---|---|
| • Results primarily from elevation of pulmonary capillary pressure secondary to LV failure<br>*LVF and RVF may occur independently or together as **'congestive cardiac failure'**. Aortic stenosis leads to chronic excessive after load and results in LVF followed by RVF, thus presenting as CCF* | • Results from imbalance between<br>- increased myocardial oxygen requirement from increased myocardial mass and intraventricular pressure (and)<br>- reduced oxygen availability | Syncope occurs due to stimulation of reflex baroceptors.<br>With exertion, the LV pressure rise stimulating these baroceptors to peripherally vasodilate.<br>*This results in an attempt to further increase cardiac output. Syncope occurs when the stenotic valve does not allow an adequate increase in cardiac output and systemic BP falls.* |

***Sudden Cardiac Death** is the fourth cardinal feature of Valvular Aortic Stenosis*
Aortic Stenosis is the most common valvular disease associated with sudden death.

**194. Answer is A (Aortic Stenosis):** *Mayo Clinic Medical Manual and Mayo Clinic Internal Medicine Review 8th/ 40 ; Practical Cardiovascular Pathology (Lippincott Williams & Wilkins, 2010)/65*

***Aortic Stenosis is the most common valvular disease associated with sudden death.***

*'The most common valve disease causing sudden death is aortic stenosis. In children subvalvular and supravalvular aortic stenosis may cause sudden death whereas in adults both congenitally bicuspid and trileaflet valves are the cause. Aortic stenosis accounts for approximately 2 percent of sudden death in adults'*

*The classic symptoms of the valvular type of aortic stenosis (regardless of type) include external dyspnoea, syncope, angina, and sudden cardiac death.* The onset of symptoms is an ominous sign. The presence of angina does not necessarily indicate coexisting coronary disease; rather, it is related to increased left ventricular filling pressure causing subendocardial ischemia. - *Mayo Clinic Medical Manual and Mayo Clinic Internal Medicine Review 8th/ 40*

**195. Answer is C (ST segment changes in ECG):** Harrison 18th/p 1939 *Harrison 17th/ 1473, 1474; O.P. Ghai 5th/ 311-312, O.P. Ghai 6th/ 418*

*'ST and T wave changes on ECG favour severe aortic stenosis' – Ghai*

***Thus ST segment changes in ECG is the answer of choice.***

- ***Ejection click*** *is not used to assess the severity of stenosis. The later having* ***the peak of ejection systolic murmur,*** *the more severe is the stenosis.*
- ***Cardiac size*** usually remains normal and so the apex though is not shifted outwards usually.
- ***$S_2$*** does not show much variation in intensity. With increasing severity the $S_2$ follows the following order normal split → single → paradoxical split

**<u>The clinical assessment of severity of aortic stenosis depends on the following:</u>** Ghai 6th/ 418

- ***Presence of Symptoms :*** ***Symptomatic patients*** *have severe Aortic stenosis however if the patient is asymptomatic it does not rule out severe Aortic stenosis.*
- *Pulse pressure :* Narrower the pulse pressure, the more sever the stenosis
- *Systolic thrill*

| Only in the suprasternal notch not at the second Rt. interspace | Systolic thrill at the second Rt. interspace | Disappearance of an earlier existent thrill |
|---|---|---|
| *Mild or critical aortic stenosis* | *Severe aortic stenosis* | *Very severe aortic stenosis* |

- *Peak of the ejection systolic murmur :* The later the peak of the ejection systolic murmur, the more severe is the *stenosis*
- *$S_2$ Split*

| Normal split | Closely split/ Normal/ Single | Paradoxical split |
|---|---|---|
| *Mild* | *Moderate* | *Severe* |

- *Presence of S4*
- *Presence of S3 indicates severe aortic stenosis with congestive cardiac failure.*
- *ECG changes : ST & T wave changes in ECG*
- *X Ray chest: Cardiac enlargement*
- *Doppler echo:* Quantitative gradient

**196. Answer is D (Delayed peak of systolic murmur):** Harrison 18th/p 1939 *Harrison 17th/ 1474; Ghai 4th/ 255, Ghai 5th/ 312, Ghai 6th/ 417*

*The ejection systolic murmur starts after the ejection click reaches a peak in midsystole.*
*With increasing severity of aortic stenosis the peak gets delayed so that the maximum intensity of the murmur is closer to the end rather than being midsystolic – Ghai*

**197. Answer is C (Aortic stenosis):** Harrison 18th/p 2004 *Harrison 15th/ 1407; Harrison 17th/ 1519; CMDT 2005/ 330*

*"Many of the traditional contraindications such as recent myocardial infarction or congestive heart failure are no longer considered if the patient is stable and ambulatory <u>but Aortic Stenosis remains a contraindication</u>" - CMDT 2005 / 333*

**Contraindications to exercise stress testing:** *Harrisons 15th/1402*

1. Acute myocardial infarction (< 4 - 5 days)
2. Rest angina < 48 hours
3. Unstable rhythm
4. Severe Aortic Stenosis
5. Acute Myocarditis
6. Uncontrolled heart failure
7. Active infective endocarditis

***Exercise testing should also not be done during an episode of unstable angina and its presence in the options confuses the issue. However, going with what CMDT has to say, aortic stenosis remains the answer of choice.***

<u>Exercise testing in unstable angina :</u> Unstable angina is a term used to describe patients who present with rapidly worsening angina, severe angina at rest or prolonged or ischaemia chest pain without ECG or enzyme evidence of MI.

Unstable angina episode → Admit, Bed Rest, Aspirin, β blockers → Exercise Tolerance test

*Exercise testing is indicated in unstable angina once the plaque has stabilized and is arranged later, in order to assess the patients need for coronary angiography if the test is positive at low work load. – Davidsons 17th / 256*

**198. Answer is A (Aortic Stenosis) :** *Harrison's 15th / 1350*

***Aortic calcification is most commonly associated with Aortic stenosis***
*Aortic Calcification in Aortic stenosis is usually apparent on fluoroscopic examination with an image intensifier or by echocardiography.*
*The absence of aortic calcification in an adult suggests that severe valvular Aortic stenosis is not present.– Harrison's*

**199. Answer is B > D (Aortic valve replacement > Observation) :** *ACC/AHA guidelines; European Cardiology Society Guidelines;* http://circ.ahajournals.org/content/122/17/1734.full.pdf+html;
http://circ.ahajournals.org/content/122/17/1734.full.pdf+html

*The patient in question has asymptomatic aortic stenosis but develops symptoms on exercise (abnormal/positive exercise test). Also the presence of mean pressure gradient of 60mm Hg put this patient into the category of 'Very Severe Aortic Stenosis' or 'Critical Aortic Stenosis'.*
***Optimal management of asymptomatic severe Aortic Stenosis continues to be a source of ongoing clinical controversy**. Surgical Aortic Valve Replacement and Watchfull waiting with frequent reassessments (observation), both continue to be legitimate though debatable treatment options.*
***Since the patient in question has 'Very Severe AS' and 'Abnormal Stress Testing' he should be considered for surgical intervention in the form of Aortic Valve Replacement (AVR).***

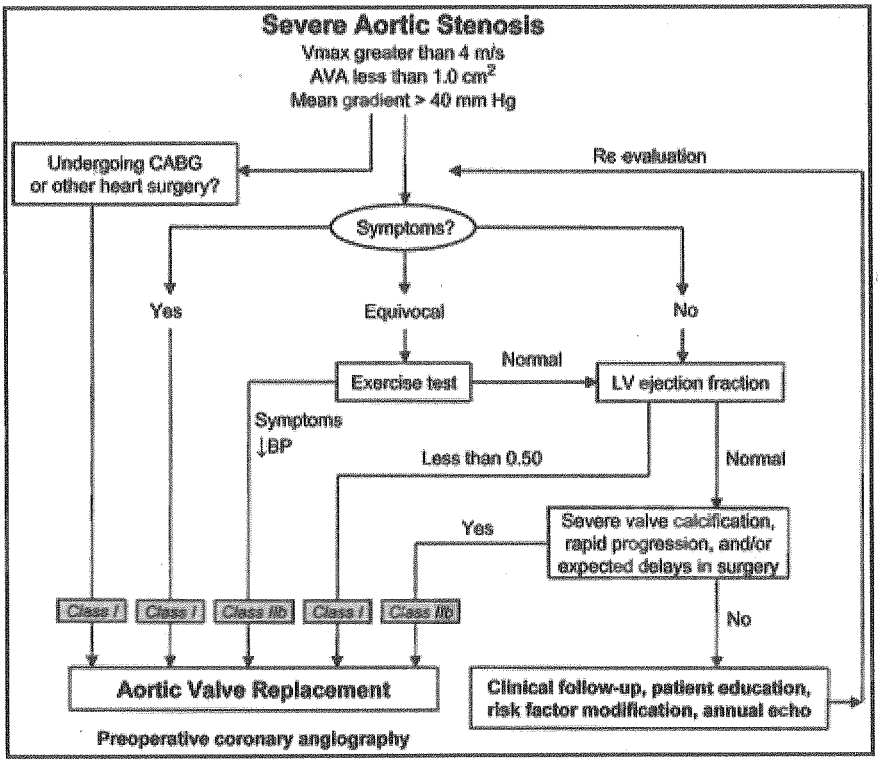
50-year-old patient with Asymptomatic Severe Aortic Stenosis

| Positive Exercise Stress Test | Mean Pressure Gradient ≥ 60 mm Hg |
|---|---|
| Symptoms during exercise such as dyspnea, angina, and syncope or near syncope constitute positive criteria indicating an abnormal stress test in patients with asymptomatic aortic stenosis. | Mean pressure gradient > 60 mm Hg and/or Aortic valve area < 0.6 $cm^2$ and /or Aortic Jet velocity > 5.0 m per second is classified as '*Extremely Severe Aortic Stenosis'* (Critical Aortic Stenosis) |
| *'Severe Aortic Stenosis with an abnormal response to exercise is considered a Class IIb indication for Aortic Valve Replacement according to the ACC/AHA Guidelines.'*<br>*'Severe Aortic Stenosis with an abnormal response to exercise is considered a Class IC indication for Aortic Valve Replacement according to European Cardiology Society Guidelines (ECS Guidelines)'* | *'Extremely Severe Aortic Stenosis (mean gradient ≥ 60 mm Hg) is considered a class IIb indication for Aortic Valve Replacement according to the ACC/AHA Guidelines.'* |

**Indications of AVR in Asymptomatic Severe Aortic Stenosis**

| Class I | Class IIb |
|---|---|
| • Patients undergoing cardiac surgery for other indications (Coronary artery bypass graft surgery or aortic surgery)<br>• Left ventricular ejection fraction <= 50 % | • ***Abnormal Hemodynamic Response to Exercise*** (Symptoms or asymptomatic hypotension)<br>• High Probability of rapid progression (Age, Calcification, Concomitant CAD)<br>• ***Asymptomatic 'very severe AS'*** (*Transaortic jet velocity >=5m/s, mean gradient >=50mm Hg, aortic valve ara <=0.6 cm2*) when operative mortality is < 1% |

*Taken from American College of Cardiology/American Heart Association Guidelines*




**Recent studies supporting AVR in 'VERY SEVER AS':**

| *Study* | *Conclusion* |
|---|---|
| *1. 'Clinical outcomes in non-surgically managed patients with very severe versus severe aortic stenosis'* *(Heart doi:0. 1136/heartjnl-2011-300137; Valvular heart disease; Original article)* | ***'Surgery should always be considered in very severe AS regardless of symptoms, and particular attention needs to be paid to their extremely poor outcomes.'*** |
| *2. 'Early Surgery Versus Conventional Treatment in Asymptomatic Very Severe Aortic Stenosis'* ('Circulation': 2010; 121: 1502-1509; Valvular heart disease; Original article) | ***'Compared with the conventional treatment strategy, early surgery is associated with improved survival by effectively decreasing cardiac mortality and sudden cardiac death in patients with very severe AS.*** *This result suggests that early surgery can be a therapeutic option to further improve clinical outcome in asymptomatic patients with very severe AS and low operative risk.'* |

**Classification of Aortic Valve Stenosis Severity**

| ***Severity*** | ***Valve Area (cm2)*** | ***Maximum Aortic Velocity (m/sec))*** | ***Mean Pressure Gradient (mm Hg)*** |
|---|---|---|---|
| *Mild* | *1.5 – 2.0* | *2.5 – 3.0* | *<25* |
| *Moderate* | *1.0 – 1.5* | *3.0-4.0* | *25-40* |
| *Severe* | *0.6-1.0* | *>4.0* | *>40* |
| *Critical (Extremely Severe)* | *<0.6* | *>5.0* | *>50-60* |

**200. Answer is C (Tricuspid valve atresia):** *Valvular Heart Disease: A Companion to Braunwald's Heart Disease by Otto (Elsevier Health Sciences, 2009)/408; CT Atlas of Adult Congenital Heart Disease (Springer, 2013)/125*

*Tricuspid Valve Atresia is not associated with Subvalvular Aortic Stenosis.*

**Subvalvular Aortic Stenosis (Subaortic Stenosis)**

- Subaortic stenosis is defined as obstruction to left ventricular outflow below the aortic valve.
- It is the second most common form of fixed aortic stenosis.
- The most common form of subaortic stenosis is 'Discrete'
  Subaortic Stenosis is further classified into 'Discrete' type and 'Diffuse Tunnel-Type' narrowing

| Types of Subaortic Stenosis |
|---|
| 'Discrete' (85 to 90 percent) : Most common form of subaortic stenosis |
| 'Diffuse' or 'Long Segment Tunnel-Type'(10%to 15% ) |

*Some have attempted to subdivide the discrete form into membranous and fibromuscular but such distinction is difficult*

- Boys are more frequently affected than girls at a ratio of approximately 2:1.
- Subaortic stenosis is associated with other cardiac abnormalities in 50% to 70% of patients
  *The two most frequently associated defects with subaortic stenosis are Ventricular Septal Defect and Coarctation of Aorta.*

| Cardiac Anomalies Associated with subaortic stenosis |
|---|
| • ***Aortic regurgitation*** |
| • *Aortic valve stenosis* |
| • *Patent ductus arteriosus* |
| • ***Coarctation of the aorta*** |
| • *Interrupted aortic arch* |
| • *Mitral valve abnormalities* |
| • ***Ventricular septal defect*** |
| • *Repaired a trioventricular septal defects* |
| • *Double-chambered right ventricle* |

- Aortic regurgitation is the most common complication of subaortic stenosis *occurring in as many as 50 percent of patients*

**201. Answer is A (Aortic Regurgitation):** *Textbook of Cardiovascular Medicine by Topol (Lippincott Williams & Wilkins, 2007) 3rd/ 511; CT Atlas of Adult Congenital Heart Disease (Springer, 2013)/125*

*Aortic regurgitation is the most common complication of subaortic stenosis.*

*Aortic regurgitation is the most common complication of subaortic stenosis occurring in more than 50% of patients. Aortic Regurgitation is believed to be caused from Valvular damage due to the high-pressure Subvalvular systolic jet originating at the level of stenosis.*

## Aortic Regurgitation

**202. Answer is B (Acute myocardial infarction):** Harrison 18th/p 1930, 1942, 1943 *Harrison 14th/ 1320, Harrisons 16th/ 1399; Harrison 17th/ 1466, 1475*

*All options other than acute myocardial infarction are known causes for acute aortic regurgitation.*

**Aortic regurgitation may result from Two Major Mechanisms : allow regurgitation of blood back into LV.**

1. *By causing valvular deformities. This is the most common cause*
2. *By deforming the aortic root.*

| Valvular disease | | | Aortic root disease | | |
|---|---|---|---|---|---|
| **Rheumatic heart disease (most common)** | ***Infective endocarditis*** [Q] | **Congenital** | **Syphilis & *Ankylosing Spondylitis*** [Q] | ***Marfan's Syndrome*** [Q] | **Idiopathic dilatation of aorta.** |
| - Thickening, deformation & shortening of Aortic valve cusps ↓ Regurgitation | Perforation or erosion of one or more leaflets ↓ Regurgitation | - Congenital bicuspid aortic valve - congenital fenestrations of aortic valve ↓ Regurgitation | Cellular infarction and scarring of 'media' of thoracic aorta leading to Aortic dilatation, aneurysm formation & Regurgitation | Cystic necrosis of media of the ascending aorta ↓ Dilatation ↓ Regurgitation | Osteogenesis imperfecta, & Severe hypertension ↓ widened aortic annulus ↓ Regurgitation |

**203. Answer is A (Acute myocardial infarction):** Harrison 18th/p 1930, 1942, 1943 *Harrisons 16th/ 1399; Harrison 17th/ 1466, 1477; See previous question.*

*Amongst the options provided Acute MI is most unlikely to produce Aortic regurgitation.*
*Acute MI is the single best answer of exclusion.*

**204. Answer is D (Pansystolic murmur):** Harrison 18th/p 1944 *Harrisons 16th/ 1400; Harrison 17th/ 1476, 1475*

**Murmur in AR :** Harrison 16th/ 1400

| Typical **diastolic murmur** of chronic AR | **Midsystolic** ejection murmur | Austin flint murmur **(diastolic)** |
|---|---|---|
| • High pitched, blowing, decrescendo diastolic murmur<br>• Heard best in the third I.C.S. along the left sternal border<br>Note: With marked post stenotic dilatation of aorta the murmur may be loudest in the 2nd or 3rd right interspace – API 7th/ 420 | • Resembles murmur of AS but is higher pitched, shorter and less rasping<br>• Heard best at the base of heart and is transmitted along the carotids | • Soft, low pitched rumbling middiastolic<br>• Heard best at the apex<br>• Produced by diastolic displacement of anterior leaflet of mitral valve by AR stream |

**205. Answer is A (A.R.):** Harrison 18th/p 1943, 1944, 3212; *17th/ 1475, 1476, 1477, 1499t, 2468*

***Arm span greater than height is suggestive of Marfan's syndrome. Aortic regurgitation (A.R.) is a feature associated with Marfans as well as consistent with a diastolic murmur is second right intercostal space.***

**Marfan Syndrome: Review**

Marfan's syndrome is a genetic disorder of the connective tissue of the body manifested principally by changes in the skeleton, eye and cardiovascular system

Mutation in the fibrillary gene [Q] (15 q 21.1) [Q]
↓
Loss of fibrillary fibre base for deposition of elastin
↓
Alteration in connective tissue in various parts of the body particularly in

**Skeletal changes of marfans syndrome:**
- *Patients are usually tall* [Q]
- *Have long limbs* [Q]
- *The ratio of upper segment to lower segment is usually **2 SDs below** the mean for age, race &sex*
- *Arachnodactyly (fingers are long and slender, spider like in appearance)* [Q]
- *Pectus Excavation, Pectum Carinatum.* [Q]
- *Scoliosis, Kyphosis* [Q]

**Cardiovascular changes** [Q]
- *Dmitral valve prolapse &* [Q]
- *Mitral valve progresses to **Mitral valve Regurgitation***
- *Aortic aneurysm occurs it can leads to **Aortic Regurgitation.***

• **Associated changes**
- *Spontaneous pneumothorax* [Q]
- *Inguinal & incisional hernias*
- *Striae may occur over the shoulders & buttocks.*

**Ocular changes** [Q]
- *Dislocation of the lens* [Q]
- *Elongation of globe (Myopia)* [Q]
- *Retinal detachment.* [Q]

**206. Answer is C (A.R.):** Harrison 18th/p 1943, 1944, 3212 *Harrison 17th/ 1475, 1476, 1477, 2468; See previous question*

***A diastolic murmur in second right intercostals space in a patient of Marfan's syndrome suggests a diagnosis of Aortic Regurgitation.***

**207. Answer is A (Aortic Regurgitation):** *Chamberlain's Symptoms and Signs in Clinical Medicine 13th/73; Clinical Examination: A Systematic Guide to Physical Diagnosis (Elsevier Health Sciences) 7TH/ 106*

***Duroziez's sign is seen in Aortic Regurgitation.***

| **Duroziez's sign in Aortic Regurgitation** |
|---|
| ***Refers to systolic and diastolic murmurs heard over the femoral artery while partially compressing the vessel with the diaphragm of the stethoscope*** |
| *A systolic murmur will be heard when the vessel is compressed with the diaphragm of the stethoscope* |
| *As the compression is increased a diastolic murmur will be heard in patients with significant aortic regurgitation (due to retrograde flow of blood back towards the heart in diastole)* |
| *Tilting the diaphragm towards the patient's heads will make the diastolic bruit softer if the patient has aortic regurgitation but louder if the bruit is due to an increased cardiac output (e.g. due to thyrotoxicosis)* |

**Selected Eponymous Signs in Aortic Regurgitation:**

| Sign | Presentation |
|---|---|
| *Becker' sign* | Prominent retinal artery pulsation |
| *Corrigan's sign* | Prominent carotid pulsation |
| *De Musset's sign* | Head nodding in time with the heart beat |
| *Duroziez's sign* | Systolic and diastolic murmurs heard over the femoral artery while partially compressing the vessel with the diaphragm of the stethoscope |
| *Gerhardt's sign* | Pulsation of the spleen in time with the heard beat |
| *Hill's sign* | Higher blood pressure (>20mmHg) in the legs than in the arms |
| *Landolfi's sign* | Rhythmic pupillary pulsation in time with the heart beat |
| *Lincoln sign* | Excessive pulsation in the popliteal artery |
| *Mayne's sign* | A fall in diastolic blood pressure (>15mm Hg ) on raising the arm above the head |
| *Muller's sign* | Pulsation of the uvula in time with the heart beat |
| *Quincke's sign* | Prominent capillary nail bed pulsation |
| *Rosenbach's sign* | Pulsation of the liver in time with the heart beat |
| *Traube's sign* | A double sound heard over the femoral artery while compressing it distally |
| *Ashrafian sign* | Pulsatile pseudo proptosis. |
| *Sherman's sign* | An easily palpable dorsalis pedis pulse in a patient over the age of 75 years. |

**208. Answer is C (Aortic incompetance):** *Harrison 15th/ 1351, 1343, Harrison 16th/ 1399; 17th/ 1476; other references.*

***Aortic regurgitation is associated with LV dilatation, LV hypertrophy and LV failure***

| | |
|---|---|
| **AR** | The total volume ejected by the ventricle (forward stroke + volume of blood that regurgitates back into L.V.) is increased in ***A.R.***<br>Also, here, the entire L.V. stoke volume is ejected into a high pressure zone, the Aorta.<br>This leads to dilatation of LV, followed by deterioration of LV function i.e. LVF;<br>Considerable thickening of LV wall (LV hypertrophy) also occurs with chronic AR. - *Harrison 14th / 1321* |
| **M.S.** | The left ventricular diastolic pressure is *normal* in isolated ***Mitral Stenosis***.<br>Mitral stenosis leads to elevated left atrial pressure, elevated pulmonary venous and capillary pressures, with resultant increase in right ventricular after load and ultimately RV failure. - *Harrison 14th / 1312* |
| **ASD** | An ***ASD*** allows shunting of blood from LA to RA and then to RV. It is Rt side of the heart that is primarily involved. No haemodynamic effects are seen on L.V. |
| **Carcinoid syndrome** | ***Carcinoid syndrome*** may cause valvular heart disease by causing endocardial fibrosis.<br>However it is the right side of the heart that is usually involved. ♀<br>Proximal side ♀ of tricuspid and pulmonary valves are involved, leading to tricuspid insufficiency or pulmonary stenosis and thereby secondary 'Right sided heart failure'. ♀ - *Harrison 14th / 586, 15th/597* |

## Pulmonic Stenosis

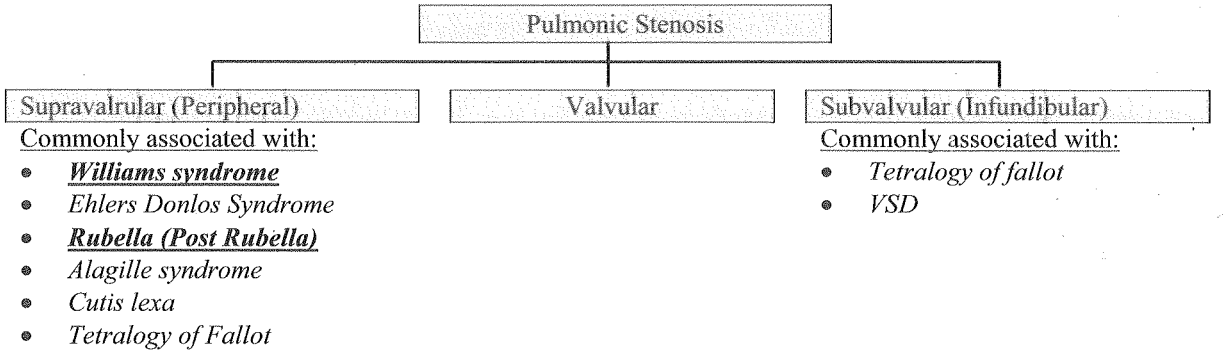
**209. Answer is D (All of the above) :** *Ghai 4th / 258, 5th/315*

***Pulmonic stenosis may occur at valvular, supravalvular and subvalvular level.***

Anatomically, Pulmonary stenosis may be located at:
1. Valvular level
2. Subvalvular level : This is also called *Infundibular pulmonary stenosis.*
3. Supravalvular level : This is also called *Peripheral pulmonary stenosis..*

**210. Answer is C and E (William syndrome and Rubella) :** *Harrisons 16th/1382, 1383; Fundamentals of Diagnostic Radiology 3rd/645*

***Peripheral pulmonic stenosis is often associated with various congenital and acquired conditions including Rubella and williams syndrome.***




**211. Answer is B (Decreases as the severity of PS increases):** *Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine*

***As the severity of pulmonary stenosis increases the interval between S1 and the systolic ejection click decreases.***

*When the pulmonary valve is thin and pliable, a systolic ejection click will be heard, which decreases on inspiration. As the severity of the pulmonary stenosis progresses, the interval between S1 and the systolic ejection click becomes shorter, S2 becomes widely split, P2 diminishes or disappears, and the systolic ejection murmur lengthens and peaks later in systole, often extending beyond A2.*

| **As the severity of the pulmonary stenosis progresses** (*Braunwald's Heart Disease)* |
|---|
| • ***The interval between S1 and the systolic ejection click becomes shorter*** |
| • *S2 becomes widely split* |
| • *P2 diminishes or disappears* |
| • *Systolic ejection murmur lengthens and peaks later in systole, often extending beyond A2.* |

## Tricuspid Regurgitation

**212. Answer is B (Dilatation of right ventricle):** Harrison 18th/p 1948 *Harrison 17th/1479 ; 16th/1402*

***"Most commonly Tricuspid Regurgitation is functional and secondary to marked dilatation of RV and the tricuspid annulus"*** *– Harrisons*

**213. Answer is A (Tricuspid Regurgitation):** Harrison 18th/p 1948 *Harrison 17th/1479*

***Systolic pulsations of the liver and marked hepatomegaly are characteristic features of Tricuspid Regurgitation.***

*'Hepatic pulsation in Tricuspid Regurgitation are caused by reversed systolic blood flow in the great veins' – 'Synopsis of Cardiac Physical Diagnosis 2nd/266'*

*'In about 2/3rd of patients with Tricuspid Regurgitation there is associated systolicpulsations of liver which may be considerably enlarged and tender' – Oxford Textbook of Medicine 4th/1012.*

**214. Answer is A (Tricuspid Regurgitation):** *Atlas of Adult Physical Diagnosis (Lippincott Williams & Wilkins) 2006/ 89; Sapira's Art and Science of Bedside Diagnosis 4th/360*

***Increase in intensity of the murmur of Tricuspid Regurgitation on squeezing the liver is called as Vitum's sign.***

| *Vitum's Sign (Maneuver of Vitum)* |
|---|
| *The examiner auscultates for the intensity of murmur of tricuspid regurgitation and gently presses on the right upper quadrant of the abdomen (Squeezes the liver). An increase in intensity of murmur suggests a diagnosis of Tricuspid regurgitation.* |

**215. Answer is A (Tricuspid Regurgitation):** *Manual of Cardiac Diagnosis (JP Medical Ltd), 2014/66; Valvular Heart Disease (Springer Science), 2010/ 89; Atlas of Adult Physical Diagnosis (Lippincott Williams & Wilkins) 2006/ 89; Sapira's Art and Science of Bedside Diagnosis 4th/360;*

***Auscultatory augmentation of Tricuspid Murmur on Inspiration is called Carvallo's sign.***

**Carvallo's Sign was described by Carvallo in 1946, as a highly diagnostic sign of tricuspid insufficiency**
Carvallo's sign was described as an inspiratory augmentation of a pansystolic/holosystolic murmur at the left lower sternal border due to increased filling of the right heart in cases of tricuspid insufficiency or tricuspid regurgitation
**Note** *However that in case of an associated right ventricular failure the intensity of murmur may not increase with inspiration (Carvallo's sign may be absent).*

**Classically described by patients in Tricuspid Regurgitation, Carvello's sign is also described in patients with tricuspid stenosis.**
The typical murmur is a low-pitched, middiastolic murmur with maximal intensity at left lower sternal border and during inspiration. This increase in intensity in inspiration is known as Carvallo's sign and ***helps to distinguish tricuspid stenosis from mitral stenosis***. An opening snap may be present.

| *Carvello's Sign in Tricuspid Stenosis* |
|---|
| *A diastolic murmur over tricuspid area which increases during inspiration (Carvallo's sign) and reduces during expiration or Valsalva manoeuvre.* |

| *Carvello's Sign in Tricuspid Regurgitation* |
|---|
| *A high pitched pansystolic murmur loudest in 4th intercostal space in the parasternal region augmented during inspiration (Carvallo's sign.)* |

**216. Answer is A (Tricuspid Stenosis):** *Manual of Cardiac Diagnosis (JP Medical Ltd), 2014/66; Valvular Heart Disease (Springer Science), 2010/ 89; Atlas of Adult Physical Diagnosis (Lippincott Williams & Wilkins) 2006/ 89; Sapira's Art and Science of Bedside Diagnosis 4th/360;*

*Carvallo's Sign representing a Diastolic Murmur that increases on inspiration is seen in Tricuspid Stenosis.*

| *Carvallo's Sign (Auscultatory augmentation of Tricuspid Murmur on Inspiration)* |
|---|
| • *Carvallo's Sign representing a Diastolic Murmur that increases on inspiration is seen in Tricuspid Stenosis* |
| • *Carvallo's Sign representing a Systolic Murmur that increases on inspiration is seen in Tricuspid Regurgitation* |

## Ischemic Heart Disease and Atherosclerosis

### Risk Factors / Atherosclerosis:

**217. Answer is C (Decreased fibrinogen levels):** Harrison 18th/p 1987 *Harrison 16th/1430, 1432; Harrison 17th/ 1505 http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=1998650&dopt=Abstract*

*Increased levels of fibrinogen (and not decreased fibrinogen levels) are associated with increased risk of atherosclerosis.*

- ***Fibrinogen Levels***
  *'Fibrinogen levels correlate with coronary risk and provide information regarding coronary risk independent of lipoprotein profile. Elevated fibrinogen levels might promote a thrombotic diathesis'. - Harrison 16th/1432*
- ***Waist Hip Ratio :*** This refers to a characteristic 'male' distribution of adipose tissue i.e. excess of fat in the abdomen compared with that in hips.
  ***'An elevated waist/hip ratio has been associated with symptomatic cardiovascular disease and cerebrovascular disease in both men and women.*** *- Pubmed (NCBI - website)*
- ***Hyperhomocysteinemia and low HDL levels*** are known risk factors for Atherosclerosis (as depicted in the following table).

| Major risk Factors for Atherosclerosis - *Harrisons 16th/1430* | Emerging risk factors |
|---|---|
| • *Cigarette smoking*<br>• *Hypertension (BP > 140/90mm/hg) or (on Antihypertensive medication)*<br>• ***Low HDL cholesterol***<br>• Diabetes mellitus<br>• Family history of CHD<br>• Age (Men > 45 years; Women ≥ 55 years)<br>• Life style risk factors<br>Obeity (BMI > 30 kg/m²)<br>Physical inactivity<br>Atherogenic diet | • Lipoprotein (a)<br>• ***Homocystine***<br>• Prothrombotic factors (Fibrinogen)<br>• Pro inflammatory factors<br>• Impaired fasting glucose<br>• Subclinical atherogenesis |

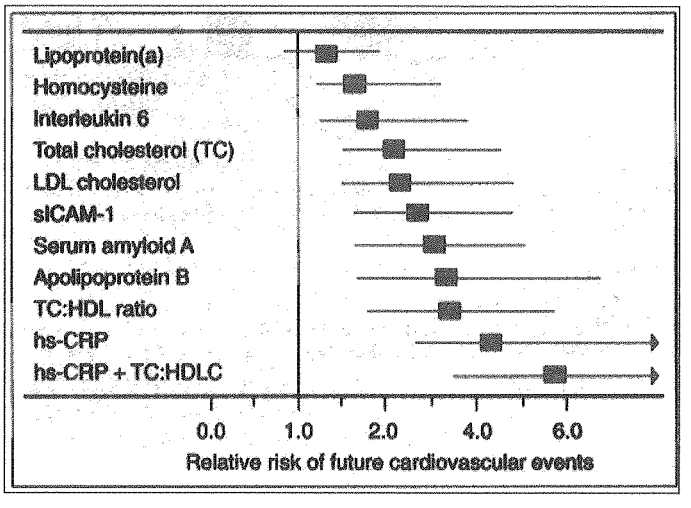
**218. Answer is A (hs CRP):** *Braunwald's 8th/1013, 1014*

***hs CRP which is a serum marker of systemic inflammation has emerged as a major risk factor marker for future cardiovascular events***

**CRP and Future risk of cardiovascular events**

- *CRP when measured by high sensitivity assays (hs CRP) strongly and independently predicts risk of Myocardial Infarction, Stroke, Peripheral Arterial disease and Sudden Cardiac Death among healthy individuals*
- hs CRP adds prognostic information at all levels of LDL cholesterol and at all levels of risk as determined by the Framingham risk score
- ***hs CRP is a better predictor of cardiovascular risk than lipoprotein 'a', homocysteine or interleukin 6 and an elevated hs CRP carries a significantly higher relative risk of future cardiovascular events than any of the other individual factors***
- Infact hs CRP may be a better predictor of cardiovascular risk than elevated LDL cholesterol levels *'Absolute vascular risk is higher in individuals with elevated hs CRP levels and low levels of LDL cholesterol than in those with elevated levels of LDL cholesterol but low levels of hs CRP'*
- hs CRP interpretation

| Hs CRP levels | Risk |
|---|---|
| <1 mg/l | Low |
| 1 – 3 mg/l | Moderate |
| > - 3 mg/l | High |




hsCRP, high reactivity C-reactive protein;
siCAM-1, soluble intercellular adhesion molecule-1;
HDLC, high density lipoprotein cholesterol

**219. Answer is A (hs CRP):** *Braunwald's 8th/1013, 1014*

*hs CRP which is a serum marker of systemic inflammation has emerged as a major risk factor marker for future cardiovascular events*

**220. Answer is B (Homocysteine):** *Harrison 18th/p 1987; Harrison 16th/1430,1432; 17th/1505; CMDT 2006/1706; 2009/1497; Ganong 22nd/623*

*'There is a strong positive correlation between atherosclerosis and circulating levels of Homocysteine'*

*- Ganong 22nd/623*

***Hyperhomocysteinemia has been most consistently linked with atherosclerosis and coronary thrombotic events***

*"Patient with clinical and angiographic evidence of coronary artery disease tend to have higher levels of plasma homocysteine. The relationship has not been extended to cerebrovascular and peripheral vascular disease"- CMDT*

*"A large body of literature suggests a relationship between **hyperhomocysteinemia and coronary events.** Several mutations in the enzymes involved in homocysteine accumulation correlate to **thrombosis** and (in some studies) **coronary risk"** -. Harrison*

***Note:***

*Major factor leading to hyperhomocysteinemia is folate deficiency – CMDT*

**221. Answer is C (Homocysteine)**

*Elevated levels of Homocysteine are associated with a significant increased risk of coronary artery disease and/or stroke.*

**222. Answer is B (LP (a))**

*Lipoprotein (a) has structural homology to plasminogen and elevated levels of Lipoprotein a (LP-a) confer a modest increased risk of CHD and Stroke.*

**Lipoprotein (a) or LP (a)**

- *It is an LDL Like plasma lipoprotein consisting of a cholesterol-rich LDL particle with one molecule of apolipoprotein B100 and an additional protein, Apo(a) apolipoprotein*
- *It that **confers a modest increased risk of CHD independent of LDL- Cholesterol.***
- *The Apo (a) apolipoprotein in Lipoprotein (a) **has structural homology to plasminogen** but lacks any fibrinolytic activity. Apo (a) may interfere with plasminogen activity and contribute to the pro-thrombotic state associated with LP (a).*
- *Lipoprotein (a) or LP (a) is **being extensively investigated as an emerging risk factor for atherosclerosis.***

**Lipoprotein (a) or LP (a) and Screening Recommendations**

*Most American Guidelines do not yet recommend measurement of Lipoprotein (a) as part of risk factor assessment however the European Atherosclerotic Society recommends screening for LP (a) in patients with intermediate or high risk of CVD/CHD.*

**The European Atheroscleosis Society Recommendations**

Recommends screening for elevated Lp (a) in those at intermediate or high CVD/CHD risk.
Recommeds a desirable level of lipoprotein(a) as <50 mg/dL,
Recommends use of niacin (1–3 g/day) for Lp (a) and CVD/CHD risk reduction.

Emerging Risk Factors with established roles in one or other Guidelines

- *Apo-B*
- *Lipoprotein(a)*
- *Homocysteine*
- *Prothrombotic Factors (Fibrinogen)*
- *Proinflammatory Factors(hsCRP)*
- *Impaired Fasting Glucose*
- *Subclinical Atherosclerosis*
  *(Ankle Brachial Plexus Index (ABPI) OR Coronary Artery Calcification assessment)*

**223. Answer is C and E:** *Harrison 18th/p 1987; Harrisons 17th/1505 : Harrisons 16th/1430, 1432*

*Increased homocysteine levels and increased lipoprotein (a) levels are risk factors for cornonary artery disease.*

Increased risk of coronary artery disease is also associated with:

- *High LDL (not low LDL)*
- *Low HDL (not high HDL)*
- *Increased Fibrinogen levels (not decreased fibrinogen levels)*

**224. Answer is B (↑ Lipoprotein B):** *Robbin's illustrated 7/e, p 520; Harrison's 16/e, p 1430-1433*

***Predisposing factors for coronary artery disease include an increased lipoprotein 'a' and not lipoprotein 'b'.***

**225. Answer is C (Atherosclerosis):** Harrison 18th/p 1987 *Harrison 17th; Ganong 20th/600*

***Raised levels of lipoprotein a is a risk factor for Atherosclerosis***

*'In addition to a high cholesterol level there is a positive correlation between atherosclerosis of coronary artery and other arteries and circulating levels of lipoprotein-(a)".*
*Lp(a) interferes with fibrinolysis by down regulating plasmin generation and thus contibutes to atherosclerosis.*

**226. Answer is C (Nephrotic syndrome)** : *Read text below*

***Nephrotic syndrome is associated with hyperlipidemia with an increased level of LDL and cholesterol in most patients. This hyperlipidemia may accelerate atherosclerosis and increase the susceptibility to coronary artery disease***

*Type V hyperlipoprotenemia is associated with normal / low levels of LDL and does not appear to increase the risk of CHD.*

**Hyperlipidemia in Nephrotic syndrome may accelerate Atherosclerosis**

- Hyperlipidemia is part of the clinical complex of Nehrotic syndrome

| **Nephrotic syndrome** is a clinical complex characterized by - |
|---|
| *Proteinuria* |
| *Hypoalbuminemia* |
| *Edema* |
| ***Hyperlipidemia / Lipiduria*** |

- Hyperlipedemia in Nephrotic syndrome is a consequence of increased hepatic lipoprotein synthesis
  ***Low density lipoproteins and cholesterol are increased in majority of patients***
  This Hyper lipidemia ***may accelerate atherosclerosis*** and progression of Renal disease - *Harrison's*

**Hyperlipidemia in Type B hyperlipoprotenemia does not appear to increase risk of CHD**

- *This disorder does not appear to increase risk of CHD* either because large trylyceride rich lipoproteins are not atherogenic or because only normal amount of LDL can be generated - *Harrison's*

| Condition | Risk Of Coronary Artery Disease |
|---|---|
| *Type I (Familial Hyper Chylomicronemia)* | *Not increased* |
| Type II A (Familial Hyper Cholesterolemia) | Accelerated |
| Type II B (Familial Combined Hyperlipidemia) | Accelerated |
| Type III (Familial Dysbetalipoprotenemia | Accelerated |
| Type IV (Familial Hyper Triglyceredemia) | Accelerated |
| ***Type V (Familial Mixed Hypertriglyceredemia)*** | ***Not increased*** |

- *Hyperlipidemia in type V hyperlipoprotenemia is not associated with increased LDL*

| **Type V hyper liprotenemia** : |
|---|
| VLDL and Chylomicrons are increased |
| LDL is normal or decreased |

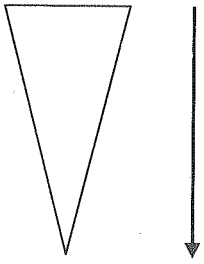
**227. Answer is A (LDL/HDL Ratio):** *Braunwald 8th/1008*

***LDH/HDL Ratio is the strongest predictor of risk of cardiovascular disease amongst the options provided***

***The ratio of either LDL cholesterol to HDL Cholesteral or Total cholesterol to HDL cholesterol is highly predictive of CHD in elderly people*** *– Essential Cardiology 2nd/6*

**Risk Factors for atherosclerosis and cardiovascular complications (Braunwald)**

- Abnormalities in plasma lipoproteins and derangement in lipid metabolism rank as the most firmly established risk factors for atherosclerosis.
- Adusted relative risk for future cardiovascular events for selected lipid fractions and lipid ratios in decreasing order are given in the following table.

| Relative risk for future cardio vascular events | Lipid Fractions and Lipid Ratios |
|---|---|
|  Decreasing Predictivity of Risk | • *Total chotesterol: HDL Cholestrol Ratio (TC: HDLC)*<br>• *Apopratein B100: HDL Cholesterol Ratio (APo B100: HDLC)*<br>• *LDL Cholesteral : HDL Cholesterol Ratio (LDLC: HDLC)*<br>• *Apoprotein B100: Apoprotein A-1 (APO B100: APO A1)*<br>• *Non HDL Cholesterol fraction*<br>• *Apolipoprotein B-1 Fraction*<br>• *HDL cholesterol Fraction*<br>• *Total cholesterol Fraction*<br>• *Apolipoprotein A1 Fraction*<br>• *LDL cholesterol Fraction* |

**228. Answer is D (LDL/HDL):** *Braunwald 8th/1008; Essential Cardiology 2nd/ 6; Refer previous quetion*

***LDL / HDL ratio is the strongest predictor of risk of cardiovascular disease, amongst the options provided***

*'The ratio of either LDL cholesterol to HDL cholesterol (LDH / HDL ratio) or Total cholesterol to HDL cholesterol (TC /HDL ratio) is highly predictive of coronary heart disease' – Essential cardiology 2nd/6*

**229. Answer is C (Chlamydia Pneumoniae):** *Inflammatory and Infectious Basis of Atherosclerosis edited by Jay Mehta (Springer) 2001 / 188*

***Evidence for Chlamydia Pneumoniae thus far presents the strongest association with human atherosclerosis.***

**Pathogens associated with atherosclerosis**

- An etiological link with atherosclerosis has been suggested with many infectious agents including Chlamydia Pneumoniae, CMV, HSV, H. Pylori and other agents.
- ***Evidence for C. Pneumonia, thus far, presents the strongest association with human atherosclerosis.***
  On the basis of sero-epidemiological pathological and laboratory data, Chlamydia Pneumoniae fulfils many of the Koch's criteria to be considered a pathogen in the genesis of atherosclerotic plaques
  - This agents can be identified in the atheromas by culture or directly by microscopy
  - This agents causes the disease on transfer to a susceptible host
  - Antibiotic therapy in some studies reduced the number of cardiovascular events. However the clinical benefits of drug therapy have not been substantiated and further large prospective studies are recommended.
- The association between CMV, HSV or H. Pylori and atherosclerosis does not fulfil the Koch's criteria that should be met to link an infectious agent with the production of the disease

**230. Answer is C (Cigarette Smoking):** *Multiple references*

***Cigarette smoking is the single most important modifiable risk factor for atherosclerosis.***

- *Smoking is the single most important modifiable risk factor for the development of Peripheral Artery Disease (PAD)*
- *Smoking cessation is the single most important target for coronary artery disease (CAD) Prevention*
- *Hypertension continues to be the most important of all modifiable risk factors for stroke*

**231. Answer is D (Avoid Alcohol):** *Braunwald 8th/1110, 1112, 1114; 'Clinical Lipidology:Companion to Brounwald's Heart Disease' 1st(2009)/203-204*

***Avoidance of alcohol is not part of dietary recommendation in patients with CHD.***

*'Moderate alcohol consumption is strongly and consistently associated with lower risk of CHD than either abstention or higher in takes. Current recommendations from AHA (American Heart Association) and the U.S. Dietary Guidelines Advisory committee are that men who drink alcohol may consume upto two alcoholic beverages per day, and women no more than one per day' – Braunwald 8th/1110*

**Saturated fats should be limited to < 7% of total calories**

Recent guidelines from AHA recommend consumption of < 7% of calories as saturated fat'-*Braunwald 8th/1112*

**NCEP – ATP III Guidelines (National Cholesterol Education Programme-Adult Treatment Panel)**

**The NCEP – ATP III guidelines** have placed major emphasis on *Therapeutic Lifestyle change (TLC)* as an essential modality in clinical management of patients at risk of CHD.
The '*Therapeutic Lifestyle Change'* Diet is designed to achieve risk reduction and makes recommendations regarding nutrient compositions in diet to reduce LDL levels and metabolic syndrome

**Nutrient Composition of the Therapeutic Lifestyle Changes Diet**

| Nutrient | Recommended Intake |
|---|---|
| Saturated fat | <7% of total calories |
| Polyunsaturated fat | Up to 10% of total calories |
| Carbohydrate | Up to 20% of total calories |
| Fiber | 20-30 g/d |
| Protein | Approximately 15% of total calories |
| Cholesterol | <200 mg/d |
| **Total Calories** | Balance energy intake expenditure to maintain desirable body weight/prevent weight gain |

**AHA recommends limiting salt intake to < 6gm/day to reduce risk of CHD**

*'Available data support the current AHA guideline of limiting salt intake to 6 gm/day, the equivalent of 100 mmol of sodium (2400 mg) per day' - Braunwald 8th/1114*

**LDL cholesterol < 100 mg/dl is recommended for patients with high risk of CHD**

*'The goal of LDL-lowering therapy in high risk patients is an LDL cholesterol level of < 100 mg/dl'*
*- 'Clinical Lipidology: A companion to Braunwald's Heart Disease' 1st (2009) /203*

**NCEP – ATP III Guidelines (National Cholesterol Education Programme-Adult Treatment Panel)**

According to NCEP-ATP III Guidelines persons are categorized *into three risk categories* depending or the presence of established CHD and risk factors. *Patients with established coronary heart disease (CHD) and CHD risk equivalents are considered high risk.*

*CHD risk equivalent's include non coronary forms of clinical at atherosclerotic disease, diabetes and multiple risk factors with 10 year risk of CHD > 20%*

The goal for LDL levels is determined by the risk category as detailed in the table below.

***For high risk patients with established CHD or CHD risk equivalents the LDL levels are targeted at < 100 mg/dl.***

| Three categories of Risk that modify Low Density Lipoprotein Cholesterol Goals | |
|---|---|
| Risk category | LDL Goal (mg/dl) |
| CHD and CHD risk equivalents | <100 |
| Multiple (2+) risk factors | <130 |
| 0-1 risk factors | <160 |

Major risk factors (Exclusive of LDL Cholesterol) that modify LDL Goals

- Cigarette smoking
- Hypertension (blood pressure ≥140/90 mmHg or on antihypertensive medication)
- Low HDL cholesterol (<40 mg/dL)
- Family history of premature CHD (CHD in male first-degree relative <55 years; CHD in female first-degree relative <65 years)
- Age (men ≥ 45 years; women ≥ 55 years)

**232. Answer is B (<200):** *NCEP – ATP III Guidelines*

*According to the* **ATP III Classification the desirable levels of total cholesterol are < 200mg/dl and optimal levels of LDL Cholesterol are < 100 mg/dl.**

**ATP III Classification of LDL, Total, and HDL Cholesterol (mg/dL)**

| LDL Cholesterol (Primary Target of Therapy) | |
|---|---|
| <100 | Optimal |
| 100-129 | Near optimal/above optimal |
| 130-159 | Borderline high |
| 160-189 | High |
| ≥190 | Very high |

| Total Cholesterol | |
|---|---|
| <200 | Desirable |
| 200-239 | Borderline high |
| ≥240 | High |

| HDL Cholesterol | |
|---|---|
| < 40 | Low |
| ≥ 60 | High |

**233. Answer is D (Omega 3 Polyunsaturated Fatty Acids);** *American Heart Association (AHA) Dietry Guidelines (2000)/http://csre.aha journals.org/cgl/content/full/02/18/2284; Braunnwald 8th/1108 http://circ.ahajournals.org/cgl/content/full/02/18*

***Consumption of Omega 3 PUFA is associated with reduced total mortality and sudden cardiac death in patients with ischemic heart disease***
***A number of studies have reported that consumption of Omega 3 fatty acids confers protection from ischaemic heart disease and that this relationship is particulary strong for coronary heart disease mortality and sudden cardiac death***
*– Branuwald 8th/1108*

**High fibre diet:** *Fibre supplements may reduce levels of total cholesterol and LDL Cholesteral, and may cause a reduction in coronary heart disease. However use of high fibre diet has not shown any benefit in overall mortality from CHD and has not yet been recommended for risk reduction in CHD by the American Heart Association (AHA)*

**Sterol Esters:** Sterol esters containing food have been documented to decrease Total Cholesterol levels and LDL cholesterol levels. They may be recommended in selected individual with hypercholesterolemia for lowering of total and LDL cholesterol levels and for secondary prevention after an atherosclerotic event.
*However the use of these agents require further monitoring as concerns have been raised regarding their tendency to decrease B cortene (vitamin A) and α-tocopherol (vit-E) levels. A clear benefit in reduction of mortality has not been documented*

**Omega 3 PUFA:** Omega 3 PUFA have been documented to decrease total mortality and sudden death in patients with ischaemic heart disease. Benefit are most prominently reported with Omega 3 PUFA's derived from marine sources, namely Eicosopentanoic acid (EPA) and ducosahexanoic acid (DHA)
***The supplemental use of Omega 3 Fatty acids (EPA plus DHA) has been recommended by the American Heart Association (Braunwald 8th/1108).***

**Pottassium Supplements:** *These agents have not been recommended by the American heart association for risk reduction in patients with coronary heart disease.*

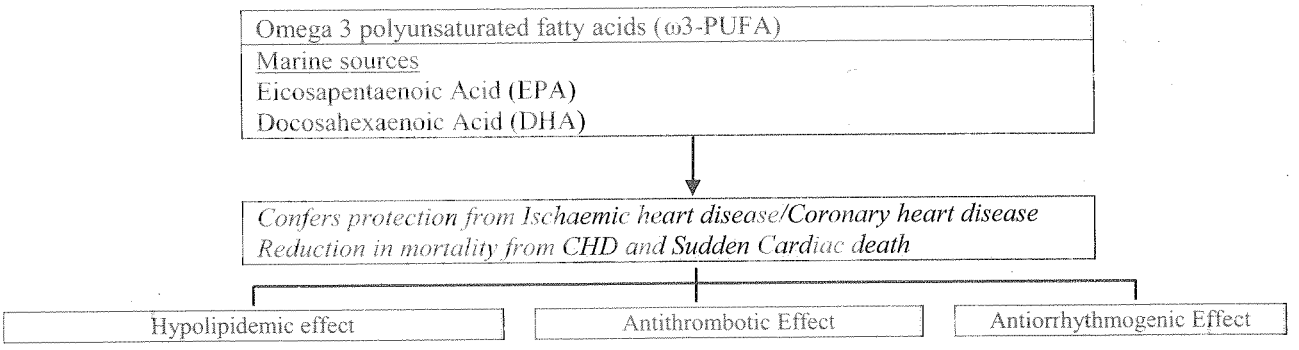
Beneficial cardiovascular effects of selected dietry components
*Preventive Cardiology by Wong, Black, and Gordon/320*

| | |
|---|---|
| • *Omega 3 Fatty, Acids* | *↓↓Triglycerides, ↓ Platelet Aggregation* |
| • *High Fibre Diet* | *↓Total cholesterol, ↓ LDL Cholesterol* |
| • *Sterol esters (Phytosterols)* | *↓ Total cholesterol, ↓ LDL Cholesterol* |
| • *Soy protein* | *↓Triglycerides, ↓ LDL Cholesterol* |
| • *Vitamin E* | *↓LDL oxidative susceptibility* |
| • *Vitamin C* | *Recycles vitamin E* |
| • *Folic Acid/Vitamin B6* | *↓Homocystine Levels* |
| • *Moderate Alcohol Consumption* | *↑HDL Cholesterol*<br>*↓Blood clotting coagulation* |

**234. Answer is C (Increased LDL and Decreased total cholesterol)**
*Comprehensive management of high tisk cardiovascular patients by cotte Toth and braunwald (2006)/367; Brawnwald 8th/1108*

*The major effect of Omega -3-polyunsaturated Fatty Acids on plasma lipids is to decrease serum triglyceride levels. They do not have a consistent effect on total cholesterol and LDL cholesterol however most studies have reported a rise in LDL cholesterol and a decreased in total cholesterol.*

***Increased LDL and Decreased total cholesterol is the single best answer of choice***




**Effect of omega 3 fatty acids on LDL levels**
*(Atherothrombosis and coronary Artery Disease by Fuste, Topel and Nobel /41)*

- *In patients with high triglycerides omega 3 PUFA cause on increase in LDL cholesterol*
- *In patients with normal triglycarides omega 3 PUFA do not decrease LDL cholesterol*
- *When omega 3 PUFA are used in place of saturated fatty Acids LDL cholesterol levels decline (but this effect is same as that found with use of other types of PUFA).*

**235. Answer is A (Intake of Unsaturated Fatty Acids is associated with decreased risk):** *Reference with text*

***Intake of Unsaturated Fatty Acids (PUFA > MUFA) is associated with decreased risk of Atherosclerosis.***

*The maximal benefit is observed with Omega 3 Poly-unsaturated Fatty Acids, however Mono-unsaturated Fatty Acids also have consistent anti-atherosclerotic benefits and both Poly-unsaturated Fatty Acids (PUFA) and Mono-unsaturated Fatty Acids (MUFA) are considered Cardioprotective Fatty Acids.*

**Hypercholestoremia alone may increase the risk of Atherosclerosis**

*'Hyperlipidemia and more specifically hypercholesterolemia is a major risk factor for atherosclerosis. Even in the absence of other factors, hypercholesterolemia is sufficient to stimulate lesion development'. – Robbins 8th/497*

**Extent of Athrosclerosis is more severe in arteries than in veins**

*Atherosclerosis is always severe in areas where pressure and velocity are high (as in arteries)* in contrast to areas where pressure and velocity are low (as in veins).
*'Overall atherosclerosis is more severe in high-pressure arteries than in pulmonary arteries with lower blood pressure. It is least severe in veins where pressure and velocity are lowest' – 'Pan – Vascular Medicine' by Topol (2002)/90*

**Abdominal Aorta is more commonly involved than Thoracic Aorta**

*'Abdominal Aorta is more commonly involved than Thoracic Aorta. Within the abdominal aorta lesions tend to be more prominent around the ostia' – 'Med Essentials' (Kaplan Publishing) 2007/249*
*'In the systemic circulation severity is accentuated in the abdominal aorta and large arteries of the lower limb where pulse wave reflection and summation effect elevate the pulse and systolic pressures. The disease is more severe in large rather than small vessels indicating the importance of mural tension and Reynolds number both of which are proportional to radius increasing the likelihood and severity of effects of blood flow disturbance at arterial forks, junctions and curvatures'.- 'Pan Vascular Medicine' by Topal (2002)/90*

**236. Answer is B (Angina Assessment)**

***WHO ROSE Questionnaire is used for assessment of Angina (often focussing on exertional chest pain)***

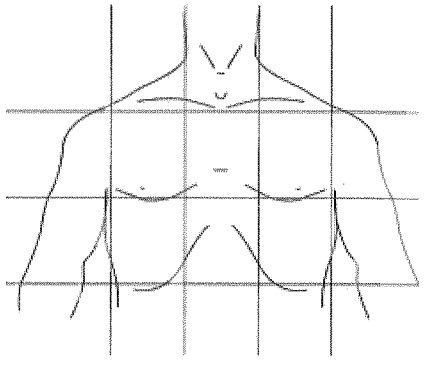
***The WHO/Rose Questionnaire was developed in 1962 for use in epidemiological (field) surveys for the assessment of ischaemic heart pain (angina) and intermittent claudication***

**The WHO Rose angina questionnaire**

The WHO Rose angina questionnaire is widely used in epidemiological studies as a standardised method for assessing angina. Rose angina questionnaire is a screening tool (rather than a diagnostic test) and was originally designed for use in men. It has been found to predict major coronary events in middle aged men and coronary heart disease mortality in both women and men.

**WHO Rose Angina questionaaire**

1. **Do you ever have any pain or discomfort in your chest?**
   Yes/No
2. **Where do you get this pain or discomfort?**
   *Please mark X on the appropriate places in the given figure*
3. **When you walk at an ordinary pace on the level does this produce the pain?** Yes/No/Unable
4. **When you walk uphill or hurry does this produce the pain?**
   Yes/No/Unable



5. **When you get any pain or discomfort in your chest on walking, what do you do?**
   Stop/Slow down/Continue at same pace/Not applicable
6. **Does the pain or discomfort in your chest go away if you stand still?** Yes/No
7. **How long does it take to go away?** 10 minutes or less / More than 10 minutes

**237. Answer is D (Three times increase in Troponin levels after Coronary Artery Bypass Grafting (CABG):** *'Universal Definition of Myocardial Infarction': Expert Consensus Document Circulation 2007 (American Heart Association Journals); 'ECS-ACCF-AHA-WHF Universal Definition of Myocardial Infarction'; http://circ.ahajournals.org/content/116/22/2634.full.pdf*

***Myocardial Infarction associated with CABG is defined by an increase in cardiac biomarkers to more than 5 times normal (> 5 times above the 99th percentile).***

**Universal Defination of Myocardial infarction**

| ***Myocardial infarction related to ischemia due to primary coronary event*** (plaque rupture) ***or imbalace between oxygen demand and supply*** (coronary spasm, hypotension etc) | ***Myocardial Infarction related Sudden Cardiac Death*** (Death occuring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood.) | ***Myocardial Infarction associated with PCI*** (in patients with normal baseline troponin values) | ***Myocardial infarction associated with CABG*** (in patients with normal baseline troponin values,) |
|---|---|---|---|
| Detection of rise and/or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile of the upper reference limit (URL) together with evidence of | *Sudden, unexpected cardiac death, involving cardiac arrest, often with :*<br>• ***Symptoms suggestive of myocardial ischaemia***, and accompanied by | • ***By convention, increases of biomarkers greater than 3 x 99th percentile*** *URL have been* | • ***By convention, increases of biomarkers greater than 5 x 99th percentile*** URL plus either new pathological Q waves |

| | | | |
|---|---|---|---|
| myocardial ischaemia with at least one of the following:<br>• Symptoms of ischaemia<br>• ECG changes indicative of new ischaemia [new ST-T changes or new left bundle branch block (LBBB)]<br>• Development of pathological Q waves in the ECG<br>• Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality. | • New ST elevation, or new LBBB, and/or<br>• Evidence of fresh thrombus by coronary angiography and/or at autopsy, | *designated as defining PCI-related myocardial infarction.* | or new LBBB, or angiographically documented new graft or native artery occlusion, or imaging evidence of new loss of viable myocardium have been designated as defining CABG-related myocardial infarction. |

**Universal Definition of Myocardial Infarction:**

**Criteria for acute myocardial infarction**

*The term myocardial infarction should be used when there is evidence of myocardial necrosis in a clinical setting consistent with myocardial ischaemia.*

Under these conditions any one of the following criteria meets the diagnosis for myocardial infarction.

- Detection of rise and/or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99$^{th}$ percentile of the upper reference limit (URL) together with evidence of myocardial ischaemia with at least one of the following:
  - Symptoms of ischaemia
  - ECG changes indicative of new ischaemia [new ST-T changes or new left bundle branch block (LBBB)]
  - Development of pathological Q waves in the ECG
  - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.
- *Sudden, unexpected cardiac death*, involving cardiac arrest, often with symptoms suggestive of myocardial ischaemia, and accompanied by presumably new ST elevation, or new LBBB, and/or evidence of fresh thrombus by coronary angiography and/or at autopsy, but death occuring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood.
- *For percutaneous coronary interventions (PCI)* in patients with normal baseline troponin values, elevations of cardiac biomarkers above the 99$^{th}$ percentile URL are indicative of peri-procedural myocardial necrosis. By convention, increases of biomarkers greater than 3 x 99$^{th}$ percentile URL have been designated as defining PCI-related myocardial infarction. A subtype related to a documented stent thrombosis is recognized.
- *For Coronary Artery Bypass Grafting (CABG)* in patients with normal baseline troponin values, elevations of cardiac biomarkers above the 99$^{th}$ percentile URL are indicative of peri-procedural myocardial necrosis. By convention, increases of biomarkers greater than 5 x 99$^{th}$ percentile URL plus either new pathological Q waves or new LBBB, or angiographically documented new graft or native artery occlusion, or imaging evidence of new loss of viable myocardium have been designated as defining CABG-related myocardial infarction.
- *Pathological findings* of an acute myocardial infarction

**Criteria for prior myocardial infarction**

Any one of the following criteria meets the diagnosis for prior myocardial infarction

- Development of new pathological Q waves with or without symptoms
- Imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract, in the absence of a non-ischaemic cause.
- Pathological findings of a healed or healing myocardial infarction.

*Taken from :Expert Consensus Document Circulation 2007 (American Heart Association Journals); 'ECS-ACCF-AHA-WHF Universal Definition of Myocardial Infarction'; http://circ.ahajournals.org/content/116/22/2634.full.pdf*

**238. Answer is A (Anterior wall of left ventricle) :** *Robbins 6th/557*

***The most common site of myocardial infarction is the anterior wall of the left ventricle.***

The frequency of critical narrowing of arterial trunks and corresponding sites of myocordial lesions are as follows :

| | | |
|---|---|---|
| Left anterior discending (LAD) (br. of LCA) | 40 to 50% (Most common) | Anterior wall of L.V. near apex<br>Anterior portion of ventricular septum |
| Right coronary artery (RCA) | 30 to 40% | Inferior/Posterior wall of L.V<br>Post. portion of ventricular septum<br>Inferior/posterior right ventricular free wall in some cases |
| Left circumflex (br. of LCA) | 15 to 20% | Lateral wall of left ventricle except the apex. |

**239. Answer is B (Left ventricle) :** *Robbins 6th / 557*

***The most common site of myocardial infarction is the anterior wall of Left ventricle.***

Anterior wall MI

| True Anterior Wall | Anteroseptal Infarction | Anterolateral infarction |
|---|---|---|
| Occlusion of Left Anterior Descending artery (LAD) | Occlusion of Left Anterior Descending artery (LAD) | Occlusion of Left coronary artery thereby causing ischemia in region supplied by LAD artery and circumflex artery (lateral wall) |

**240. Answer is A (Anterior wall):** *Repeat*

***The most common site of myocardial infarction is the anterior wall of left ventricle.***

**241. Answer is D (Marginal artery):** *Robbin's 7th/577-578; Snell's 7th/117-119*

***Marginal branches are not commonly involved.***

The frequency of critical narrowing of arterial trunks

| Common | Uncommon | Rare (Never Encountered) |
|---|---|---|
| • Left anterior descending (LAD) artery (40-50%)<br>• Right coronary artery (30-40%)<br>• Left circumflex coronary artery (15-20%) | • Left main coronary artery<br>• Secondary branches e.g.<br>- Diagonal branches of LAD artery<br>- ***Marginal branches*** | • Penetrating intramyocardial branches of coronary arteries |

**242. Answer is C (Tall T waves with increased amplitude):** *Harrison 18th /1836*

***Acute myocardial infarction is associated with 'ST segment' elevation and tall, positive, hyperacute T waves (increased amplitude of T waves).***

*'When the acute ischemia is transmural, the ST vector usually is shifted in the direction of outer layers (epicardial), producing ST elevation and sometimes in the earliest stages of ischemia, tall, positive so called hyperacute T waves over the ischemic zone'- Harrison's 18th / 1836*

**E.C.G. changes in acute infarction**

| Early acute phase *(within hours)* | Fully evolved phase | Old infarction *(resolution phase)* |
|---|---|---|
| • *Elevation of ST segment*<br>• ***Tall wide (peaked) T wave*** | • *Pathological Q wave*<br>• *Elevated ST segment beings to resolve*<br>• *T wave inverts* | • *Pathological Q wave*<br>• *ST segment and T wave may be normal* |

**243. Answer is B (Left Circumflex (LCx)):** *References with text*

***Ischemia in the distribution of Left Circumflex Artery is difficult to detect on standard 12 lead ECG.***

'*Circumflex distribution ischemia is notoriously silent on an ECG as the posterolateral wall is under-represented on a conventional 12 lead ECG' – 'Manual of cardiovascular medicine' by Griffin 3rd/528*

*'A normal ECG does not exclude acute MI especially when the Left circumflex is the culprit vessel because most of the area supplied by the LCx is not represented in the standard 12 lead ECG'*
*– 'Basic and Bedside Electrocardiography' by Baltazar (Lippincott Williams, 2009) 1st /344*

'*Acute Myocardial Infarctions in the distribution of the circumflex artery are likely to have non diagnostic* ECG'
*– 'Management of Acute Coronary Syndromes' by Cannon (2003) /213*

*There are areas of the heart that are difficult to 'see' with the ECG particularly in the left circumflex distribution Small areas of ischemia may be missed altogether – 'Cardiovascular Biomarkers' by Morrow (2006)/182*

'*The posterolateral wall of the LV tends to be electrocardiographically silent. Occlusion of a small circumflex artery may not cause ST segment elevation in lateral leads (Leads I, aVL and / or $V_{5-6}$).Occasional patients with posterolateral MI have no ECG changes at all. Infact patients who are having MI without ECG changes usually have a posterolateral infarction' – Primary Care Cardiology' by Taylor 2nd/139*

'ECG *may be normal in high lateral wall infarctions as this area may be electrocardiographically 'Silent'*
*– 'Critical care Medicine : The Essentials' (2009)/385*

**244. Answer is E (Lead $V_5$):** *Yao & Artusio's Anesthesiology 6th/149, 150; Foundations of Anesthesia by Hemmings & Hopkins 2nd/ 160, 161; Cardiac Surgery in the Adult by Cohn 3rd/285*

***The most sensitive lead in detecting intraoperative myocardial ischemia is lead $V_5$***

*'If only one lead can be displayed V5 should be used because V5 has the greatest sensitivity: 75% intraoperatively and 89% during exercise treadmill testing'-Yao & Artusio's Anesthesiology: Problem Oriented Patient Management 6th/-150*

Most sensitive leads in detecting Intraoperative Myocardial Ischemia

| If only one lead can be displayed | If two Leads can be displayed | If three leads can be displayed |
|---|---|---|
| Lead $V_5$ | Lead $V_4$ and $V_5$ (~90%)<br>Lead II and $V_5$ (>80%)<br>(some studies have shown ~90% sensitivity with leads II & $V_5$) | Lead II, $V_4$ & $V_5$<br>(~ 96% sensitivity) |

*Lead $V_5$ has the greatest sensitivity in deteting intraoperative myocardial ischemia*

***Traditionally Lead II and $V_5$ have been used to monitor intra operative myocardial ischemia with reported sensitivities of ≥90%. However more recent studies rare shown the combined sensitivity of Lead II & V5 to be about 80% whereas combining V4 & V5 increased sensitivity to 90%.***

**245. Answer is B (Unstable angina):** *Harrison's: 18th/ 1836-37*

***Wellen's syndrome suggests Unstable Angina.***

*Wellens' syndrome (or Wellen's sign) is an electrocardiographic manifestation of critical proximal left* ***anterior*** *descending (LAD) coronary artery* ***stenosis*** *in patients with* ***unstable angina****. It is characterized by symmetrical, often deep (>2 mm), T wave inversions in the* ***anterior precordial leads****. Wellens syndrome is also referred to as LAD coronary T-wave syndrome. Recognition of Wellen's ECG abnormality is significant because this syndrome represents a preinfarction stage coronary artery disease (CAD) that often progresses to a devastating anterior wall MI.*

**246. Answer is A (Anterolateral wall):** *Chandrasoma Taylor 3rd/ 361; Robbins illustrated 6th/ 557; 7th/578*

***Occlusion of anterior descending branch of left coronary artery leads to infarction of anterior wall of LV with or without involvement of the septum*** *– Chandrasoma Taylor 3rd/ 361*

**The site of involvement of Arteries and the corresponding sites of myocardial lesions**:

| Left anterior descending artery (40-50%) | Right coronary artery (30-40%) | Left circumflex artery (15-20%) |
|---|---|---|
| • *Anterior wall of left ventricle near apex*[Q]<br>• *Ant. portion of ventricular septum*[Q]<br>• *Apex Circumferentially*[Q] | • *Inf. post. wall of left ventricle*[Q]<br>• *Post. portion of ventricular septae*[Q]<br>• *Inf. post. right ventricular free wall in some cases*[Q] | • *Lateral wall of left ventricle except at apex*[Q] |

**247. Answer is A (An ECG):** *Harrison 18th/p 2001; Harrison 16th/1449-1450; Harrison 17th/ 1517*

***The patient in question may well be suffering from an acute myocardial infarction. An ECG to exculde an acute MI should be the initial Investigation.***

***'Presence of Epigastric pain in association with breathlessness and evidence of parasympathetic overactivity (bradycardia and hypotension) suggests the diagnosis of an acute (inferior) MI.' ECG therefore should be done as an initial investigation to exclude / confirm a diagnosis of acute MI.'***

The following lines from Harrison give away the answer to the question :

- 'Typically the pain involves the central portion of chest and / or epigastrum'.
- 'The frequent location of the pain beneath the xiphoid and patients denial that they may be suffering a heart attack are chiefly responsible for the common mistaken impression of indigestion.
- In the elderly, MI may present with sudden onset breathlessness.
- Although many patients have a normal pulse and blood pressure about one fourth of patients with anterior infarction have manifestations of sympathetic nervous system hyperactivity (tachycardia and / or hypertension) ***and upto one half with inferior infarction show evidence of parasympathetic hyperactivity (bradycardia and / or hypotension)***.

**248. Answer is D (The levels of cardiac markers remain unchanged):** *Harrison's 15th/ 1401; Harrison 16th/1444; Chandrasoma Taylor 3rd/ 366*

***Necrotic myocardial fibres release a variety of enzymes into blood stream.***
***In stable angina necrosis of the cell does not occur so there is no elevation of serum enzymes.***

| Stable angina | Unstable angina | Variant angina (Prinzemetal angina) |
|---|---|---|
| • Chest pain or arm discomfort on effort that is<br>- relieved within 5' – 10 minutes by rest and or sublingual nitroglycerine.<br>- Reproduced by physical exertion or stress<br>• No elevation of cardiac enzymes | • Anginal pain or discomfort when<br>- it occurs at rest usually lasting > 10 min<br>- it becomes distinctly more severe, prolonged or frequent (crescendo pattern)<br>• No elevation in cardiac enzymes | • Anginal pain that occurs at rest, not related to excretion, with transient ST elevation and is produced due to focal spasm of an epicardial coronary artery leading to severe myocardial ischaemia.<br>• Small elevations of cardiac enzymes may occur. |

***When a patient with unstable angina develops elevated cardiac biomarkers a diagnosis of Non ST-elevation MI is established.***

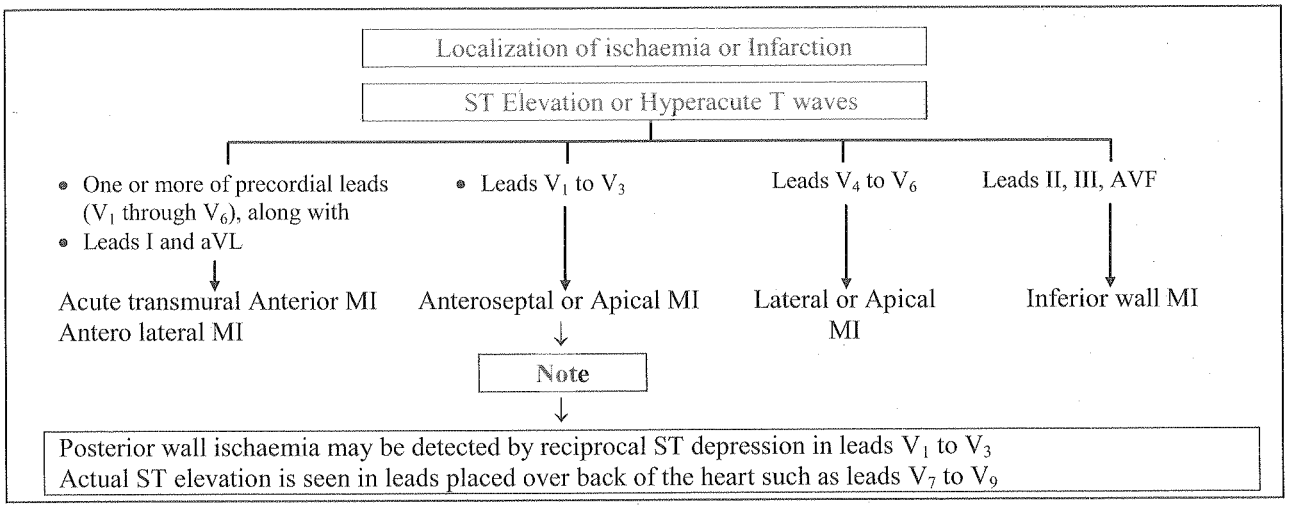
**249. Answer is C (ST segment elevation):** Harrison 18th/p 2023 *Harrison 17th/ 1533; Read text below; Repeat*

**E.C.G. changes in acute infarction**

| **Early acute phase** *(within hours)* | **Fully evolved phase** | **Old infarction** *(resolution phase)* |
|---|---|---|
| • *Elevation of ST segment*<br>• *Tall wide (peaked) T wave* | • *Pathological Q wave*<br>• *Elevated ST segment beings to resolve*<br>• *T wave inverts* | • *Pathological Q wave*<br>• *ST segment and T wave may be normal* |

**250. Answer is A (Anterolateral wall MI) :** Harrison 18th/p 1836 *Harrisons 17th/1393 Braunwald 8th/176*

***Acute transmural Anterolateral wall ischaemia is associated with changes in one or more of the precordial leads (V1 through V6) and in leads I and aVL.***




**251. Answer is A (Troponins):** *Harrison's 18TH/ 2016, 2024 ; Harrison's 16th/ 1451*

***Cardiac Troponins are the biomarkers of choice for detection of Acute Myocardial Infarction.***

*The enzymes troponin I and troponin T are normal proteins important in the contractile apparatus of the cardiac myocytes. They are released into the circulation about 4-8 hours after myocardial infarction and are still detectable for 10-14 days after the initial event.* ***The long half-life allows for the late diagnosis of myocardial infarction*** *(however makes it difficult to detect re-infarction as can occur in acute stent thrombosis after percutaneous coronary intervention).*

**Preferred Markers for Detection of Acute Myocardial Infarction (Specific)**

| Enzyme | Seen at | Peaks at | Returns to normal after | Other features |
|---|---|---|---|---|
| Creatinine phosphokinase (MB Isoenzyme) | 4 to 8 hours | 24 hrs | 48-72 hrs | • Very sensitive test<br>• Less specific than troponins (also increase in skeletal muscle injury)<br>• ***Test of choice for detecting recurrent ischemic event in 4 to 10 day window*** |
| Troponin I | 4 to 8 hours | 48 hours | 7-10 days | • Very Sensitive test (Sensitivity similar CPK-MB)<br>• Very Specific test (More specific than CPK-MB).<br>• ***Test of choice for detecting Acute Myocardial Infarction (Early diagnosis and Late Diagnosis)***<br>• ***Less useful for detecting re-infarction since troponins may remain elevated for 10-14 days making it*** |
| **Troponin T** | **4 to 8 hours** | **48 hours** | **10-14 days** | |

**Non Specific Markers for Detection of Acute Myocardial Infarction ( Not Preferred)**

| Enzyme | Seen at | Peaks at | Returns to normal after | Other features |
|---|---|---|---|---|
| Myoglobin | 30 minutes to 2 hours | 4-6 hours | 10 to 12 hours | ***Earliest Marker to be raised***<br>Not specific for MI |
| Lactate dehydrogenase | 24 hrs | 4-5 days | 10 days | Not Specific |
| AST or SGOT | Within 12 hrs | 48 hrs | 4-5 days | Not specific |

**252. Answer is B (CK-MB):** *Harrison 16th/ 1451*

***CK-MB is the Cardiac Biomarker of Choice for diagnosis of Re-infarction 8 days after the initial ischemic event.***

*The CK-MB level will increase approximately 4-8 hours after a myocardial infarction and return to normal after 72 hours (3 days). This makes it useful for the detection of re-infarction in the 4-10 day time window after the initial insult since troponins may remain elevated for 10-14 days making it less useful for this purpose.*

**253. Answer is C (Creatinine phosphokinase):** *Chandrasoma Taylor IIIrd / 365;*

***Creatinine phosphokinase is seen at 4 to 8 hours (May be seen at 2-4 hours), peaks at 24 hours and return to normal by 72 hours.***

**Creatinine phosphokinase MB (CPKMB)**

- **Very sensitive** (*CPK MB isoenzyme increases the specificity)*
- *'Absence in change in levels of CPK and CPKMB during the 1st 2 days essentially excludes the diagnosis of MI' – Chandrasoma*
- *CK elevation used to be test of* **choice** *in First 24 hours.* ***('Cardiac troponins are now preferred').***
- *CKMB is still the test of choice for detecting recurrent ischaemic event.*

**254. Answer is B (Cardiac troponins):** Harrison 18th/p 2016, 2023, 2024 *Harrison 16th/ 1451; Harrison 17th/ 1528, 1534*

*'Cardiac troponins are now the preferred biochemical markers for MI' – Harrison's 16th/ 1450*

**Cardiac troponins**

- Cardiac specific troponin T and cardiac specific troponin I are now the preferred biochemical markers for MI – Harrisons 16th/ 1451
- Many hospitals are now using cTnT or cTnI rather than CkmB as routine serum cardiac marker for diagnosis of AMI.
- They are not normally detectable in blood of a healthy individual but may increase after myocardial infarction to levels over 20 times higher
- They are particularly valuable where there is clinical suspicion of either skeletal muscle injury or a small myocardial infarction that may be below the detection limit of CK and CKMB.

| Marker | Rise | Remains elevated for |
|---|---|---|
| Troponin I | Within 4-8 hours | 7-10 days |
| Troponin T | Within 4-8 hours | 10-14 days |

**Creatinine phosphokinase:**

- 'CK-MB' was until recently considered the test of choice in diagnosis of acute MI in first 24 hours.
- The CK-MB isoenzyme may be elevated following cardiac surgery, myocarditis, and electrical cardioversion and therefore many hospitals are now using. Cardial troponins rather than CK MB as the routine serum cardiac marker for diagnosis of MI.

**Myoglobin**

- It is one of the first markers to increase after MI.
- It is however non specific returns to normal within 24 hours.

**255. Answer is D (Myocardial infarction):** *Robbin's 7th/557*

***Troponin T is a marker of Myocardial infarction.***

**256. Answer is C (Reinfarction after four days):** *Harrison 18th/p 2024; 16th/ 1450, 1451; 17th/ 1534*

***Because cardiac troponins are elevated for prolonged periods (> 1 week) an episode of recurrent ischaemia after four days would be more readily diagnosed with a marker that remains elevated in blood more briefly such as cKMB which returns to normal levels by 72 hours.***

**Limitation of troponin measurements :**

*Because these markers remain elevated for prolonged periods (> 1 week) episodes of recurrent ischemic discomfort and suspected recurrent MI are more readily diagnosed with a serum cardiac marker that remains elevated in the blood more briefly such as CKMB or myoglobin. – Harrison 16th/ 1451*

**257. Answer is B (Troponin T/I):** *Harrison 18th/2023, 2024; 'Point-f-Care Testing' 2nd/305; 'Cardiac Markers' by Wu (Humana Press) 1998/120, 121*

***Cardiac specific Troponins (Troponin T and Troponin I) are the biochemical markers of choice for detection of Acute MI in both healthy individuals as well as atheletes.***
*'The measurement of cTnT and cTnI (cardiac specific Troponin T & I) is of considerable diagnostic usefulness and they are now the preferred biochemical markers for MI' – Harrison's 18th/2023*

**CK-MB isoenzyme is not a sensitive marker for AMI in Athletes**

- The MB isoenzyme of CK has the advantage over total CK that it is not present in significant concentration in extracardiac tissue and therefore is considerably more specific. CK-MB rises within 4-8 hr after Acute MI and elevated *CK-MB is accepted as a sensitive marker for diagnosis of Acute Myocardial Infarction in healthy individuals.*
- *Individuals who train for long distance races (Athletes like marathan runners) however have been observed to have very high resting concentration of CK-MB in skeletal muscles.* This may be owing to an adaptation by the athelete to produce a higher relative content of CKMB within skeletal muscles themselves.
- *Studies of CK-MB levels in trained marathan runners have reveaked that total CK and percentage of MB isoenzyme is asymptomatic runners have been comparable to levels of CK and CKMB in patients with myocardial Infarction.*

> *'Because of nonspecificity of CKMB fraction in runners (atheles) the measurement of this isoenzyme is of little value in making an early diagnosis of myocardial injury in athelets. A measurement of troponin I is much better because it is specific for cardiac injury' – 'Point-of-Care Testing' 2nd/305*

**258. Answer is B (Hibernating Myocardium):** *'Panvascular Medicine' by Topal (Springer) 2002/735; 'Ischemic Heart Disease' by Falk (Manson Publishing)/2010/46, 47; 'Stress Echocardiography' by Picano (Springer) 5th/274*

***The contractile function of Hibernating Myocardium can be completely restored after reperfusion.***

*'Hibernating Myocardium is a reversible state of contractile dysfunction observed in the course of chronic ischemia associated with reduction of coronary blood flow without major evidence of irreversible myocardial damage (viable myocardium). The contractile function of the hibernating myocardium can be almost completely restored after reperfusion (revascularization)' – 'Panvascular Medicine' by Topal (Springer) 2002/735*

| Stunned Myocardium | Hibernating Myocardium |
|---|---|
| • 'Stunned Myocardium refers to a state of post-ischemic '*reversible*' myocardial contractile dysfunction ***that persists despite myocardial reperfusion.*** | • Hibernating myocardium refers to a state of ischemic (chronic) *reversible* myocardial contractile dysfunction ***that is almost completely restored after myocardial reperfusion.*** |
| • Myocardial stunning essentially describes the post-ischemic metabolic and contractile compromise in viable myocardium after a transient coronary occlusion (i.e. post successful reperfusion in AMI). | • Myocardial Hibernation essentially describes a chronic state of contractile dysfunction at rest in non-infarcted viable myocardium as a result of persistently reduced blood flow, which has the potential to improve function after restoration of myocardial blood supply. |
| • In stunned myocardium contraction does not return to baseline for a prolonged period of time after restoration of blood supply and the eventual recovery of contractile dysfunction is believed to be 'spontaneous'. | • In Hibernating myocardium the eventual return of contractile dysfunction is believed to be directly related to myocardial reperfusion/revascularization. |
| • Stunned myocardium is typified by a normal or near normal regional blood flow and represents a mismatch between flow and function. | • Hibernating myocardium is typified by reduced regional blood flow and reduced flow matches contractile dysfunction. |

| Conceptual model of myocardial stunning | Conceptual model of hibernating myocardium |
|---|---|
| **Acute** coronary occlusion<br>↓<br>Ischemic ventricular dysfunction<br>↓<br>*Early reperfusion*<br>↓ Inotropic Stimulation<br>*Persistent ventricular Dysfunction* → Improved ventricular function<br>↓<br>Delayed spontaneous recovery of ventricular function | **Chronic** severe coronary stenosis<br>↓<br>Chronic reduction in blood flow and ischemia<br>↓<br>Myocardial metabolic adaptation<br>↓ Inotropic Stimulation<br>Chronic contractile dysfunction → Improved Contractile function<br>↓ Revascularization<br>Improved contractile function |

| Features | Stunned Myocardium | Hibernated Myocardium |
|---|---|---|
| Resting function | Depressed | Depressed |
| *Flow* | *Normal/Increased* | *Decreased/Normal* |
| Coronary anatomy | Any | Severe stenosis or occlusion |
| Duration | Hours to days | Days to months |
| ***Recovery*** | ***Spontaneous*** | ***After revascularization*** |
| Clinical significance | Prognostic | Therapeutic |
| Clinical models | Acute myocardial infarction | Ischemic cardiomyopathy |

**259. Answer is B (Nitrates):** *CMDT 2002/ 392; 2008/ 307; CMDT 2009/316; Harrison's 16th/ 1448; Harrison 17th/ 1531*

***"Sublingual nitroglycerine is the drug of choice"*** *– CMDT*

Nitrates decrease arteriolar and venous tone, reduce preload and afterload, and reduce the oxygen demand of the heart. Nitrates may also improve myocardial blood flow by dilating collateral channels in the presence of increased vasomotor tone, or coronary stenosis.

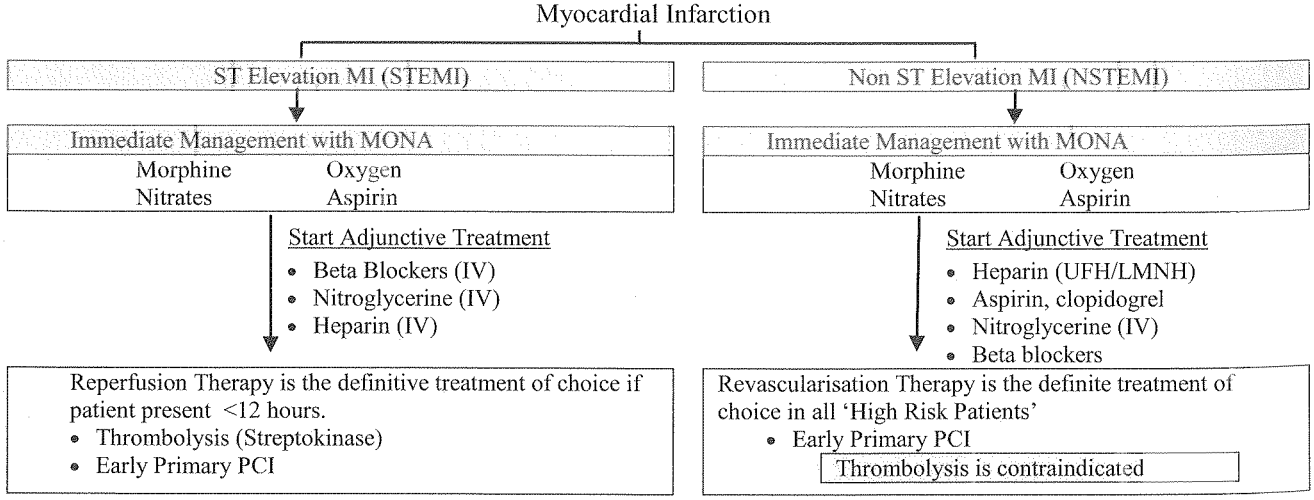
**Indications of agents used in Prinzemetal angina :**

| | | |
|---|---|---|
| Sublingual nitroglycerine | : | Abolish episodes of variant angina promptly |
| Long acting nitrates | : | Useful in preventing recurrences. |
| Calcium channel blockers | : | Extremely effective in prevention of coronary artery spasms of prinzemetal angina. |
| Beta blockers | : | Response is variable |

**260. Answer is C (Early Primary coronary intervention):** Harrison 18th/p 2027*; 17th/1537; Braunwald 8th/1233 to 1333*

*Streptokinose (Thrombolysis) is a form of Reperfusion therapy that is indicated for only ST Elevation MI (STEMI). Its use is contraindicated in cases of Non ST Elevation MI (NSTEMI)*

***Early Primary Coronary Intervention (Early PCI) can be used as a form of Reperfusion therapy for both STEMI and NSTEMI. Early Primary Caronary Intervention is therefore the single best answer of choice amongst the options provided.***



**261. Answer is B (1.5 million units):** *Harrison 18th/1001*

***The adult dose of streptokinase for Acute Myocardial Infarction is 1.5 million U IV over 60 minutes***
(Given in 50 mL of 5% dextrose in water - D5W)

| Thrombolytic drugs used in Acute Myocardial Infarction | |
|---|---|
| Drug for Acute Myocardial Infarction | Dose |
| **Streptokinase**<br>*Streptokinase usually cannot be administered safely a second time within 6 months, because it is highly antigenic results in high levels of antistreptococcal antibodies.* | The adult dose of streptokinase for Acute Myocardial Infarction is 1.5 million U in 50 mL of 5% dextrose in water (D5W) given IV over 60 minutes. |
| **Alteplase**<br>*Alteplase* was the first recombinant tissue-type plasminogen activator (is identical to native tPA)<br>*Alteplase is fibrin-specific and has a plasma half-life of 4-6 minutes.* | Accelerated infusion of alteplase for AMI consists of a 15-mg IV bolus followed by 0.75 mg/kg (up to 50 mg) IV over 30 minutes and then 0.5 mg/kg (up to 35 mg) IV over 60 minutes. |
| **Reteplase**<br>*Reteplase* is a second-generation recombinant tissue-type plasminogen activator that seems to work more rapidly and has a lower bleeding risk than the first-generation agent alteplase.<br>Reteplase is FDA-approved for AMI | Administered as 2 boluses of 10 U given 30 minutes apart. Each bolus is administered over 2 minutes. |
| **Tenecteplase**<br>*Tenecteplase,* the latest thrombolytic agent produced by recombinant DNA technology approved for use in clinical practice<br>Tenecteplase has a half-life ranging initially from 20-24 minutes to 130 minutes for final clearance, mostly through liver metabolism. | Tenecteplase is administered in a 30-50 mg IV bolus over 5 seconds. |

**262. Answer is B 10 IU:** *Harrison 18th/1001*

***The recommended dose for Reteplase in Acute Myocardial infarction is 10 Unit bolus given over 2 minutes. It is recommended to repeat the second 10 Unit dose after 30 minutes. Two bolus doses given 30 minutes apart are recommended (Total 20 Units).***

**263. Answer is B (6 minutes):** *Harrison 18th/1001*

***Alteplase has a plasma half-life of 4-6 minutes.***

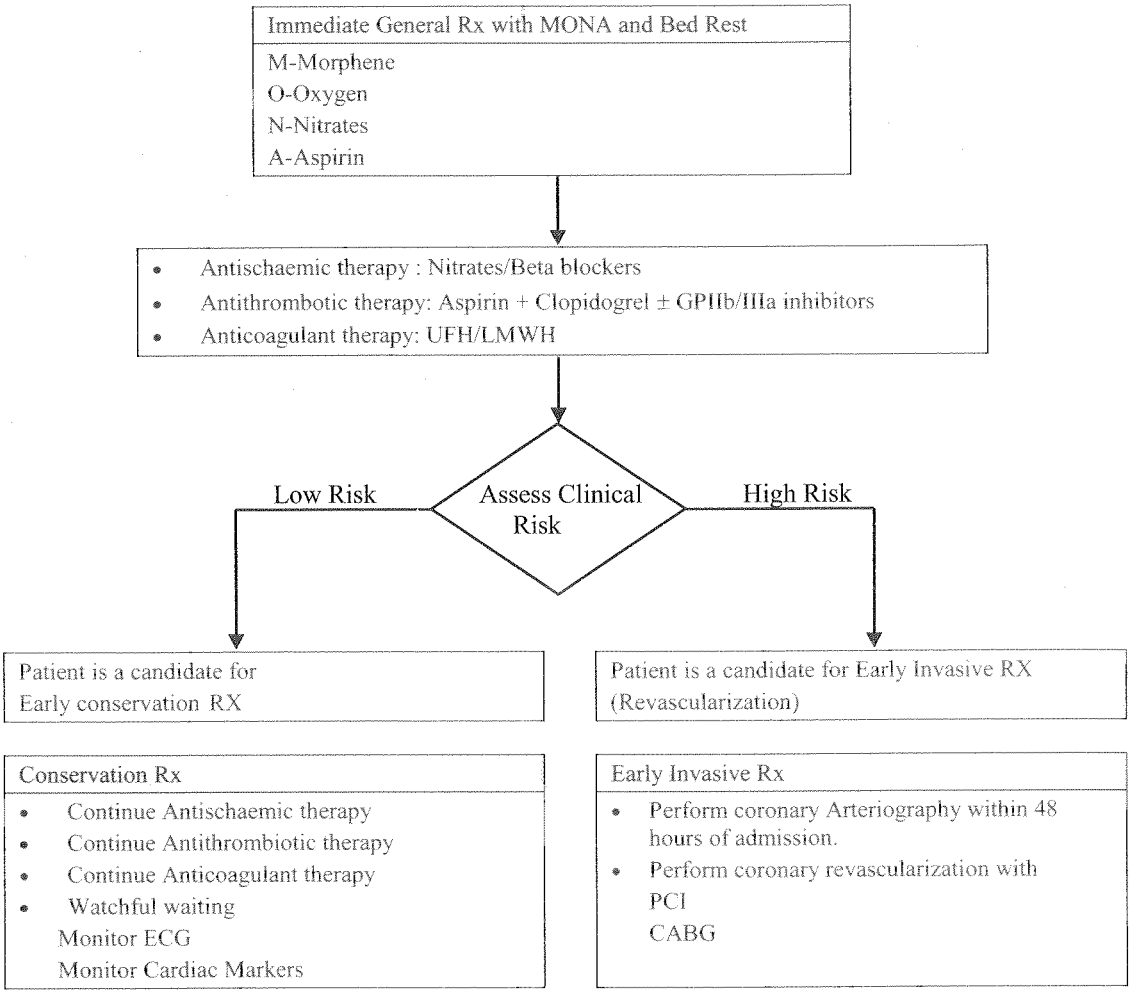
**264. Answer is B (Early Revascularization with PCI):** *Refer text below*

*The patient presenting as a case of NSTE MI to the emergency department.*

*The presence of elevated cardiac troponins and history of previous PCI place the patient into a high 'risk category'.*

***The Patient in question is thus a 'high risk' patient with NSTEMI***
***Such patients are candidates for early invasive management with PCI/CABG.***

**Management of NSTEMI**




**265. Answer is D (Lidocaine by Bolus infusion):** Harrison 18th/p 2016-2020 *Harrison's 15th/ 1408, 16th/ 1446, 1447; 17th/ 1529, 1530, 1531*

***This patient with several risk factors for ischaemic heart disease and chronic exertional dyspnea now develops 'several daily' episodes of chest pain and 'pain at rest' suggesting a diagnosis of U.A (or NSTEMI). While nitrate are recommended as the initial antiischaemic treatment, aspirin and heparin form part of antithrombotic treatment. Lidocaine is not indicated.***

**Unstable angina** is defined as angina pectoris or equivalent ischaemic discomfort with at least one of three features:

1. it occurs at rest or with minimal exertion usually lasting > 10 min.
2. it is severe and of new onset (i.e. within the prior 4-6 weeks)
3. it becomes distinctly more severe prolonged or frequent then previously i.e. crescendo pattern.

**Non ST elevation MI:** If a patient with clinical features of unstable angina develops evidence of myocardial necrosis (elevated cardiac enzymes) a diagnosis of NSTEMI is established.

**Management of unstable angina/ NSTEMI**

**Patient with U.A. / NSTEMI**

↓

Bed rest with continuous ECG monitoring

| Anti ischaemic treatment | Anti thrombotic therapy |
|---|---|
| Initial treatment should include nitrates and β blockers to provide relief and prevent recurrence.<br>• Nitrates<br>• Beta blockers<br>• Ca channel blockers: Patients whose symptoms are not relieved by adequate dosage of nitrates and β blockers<br>• Morphine sulphate: patients whose symptoms are not relieved after three sublingual nitroglycerine tablets or whose symptoms reoccur with adequate anti ischaemic therapy | Initial therapy should begin with platelet cyclooxygenase inhibitor aspirin either isolated or in combination with clopidogrel (platelet adenosine receptor blocker)<br>• Oral antiplatelet therapy<br>- Aspirin - Clopidogrel.<br>• Heparins<br>• Intravenous antiplatelet therapy<br>- Abciximab<br>- Eplifibatide<br>- Tirofiban. |

**266. Answer is A (Intra-aortic balloon pump and PCI):** *Harrison's 18th/2234; Goldman's Cecil Medicine 24th/chapter 107*

*Cardiogenic shock in Acute MI is an indication of IABP Counterpulsion. The treatment of choice for a patient of Acute ST Elevation Myocardial infarction with cardiogenic shock is mechanical circulatory support with IABP followed by emergency coronary angiography and revascularization with Primary Coronary Angioplasty or CABG (Under IABP Support).*

Intra-aortic balloon pump (IABP) is recommended when shock is not quickly reversed with pharmacological therapy, as a stabilizing measure for patients who are candidate for further invasive care. IABP is useful as a stabilizing measure in patients before and during cardiac catheterization and percutaneous coronary intervention (PCI) or before urgent surgery. IABPs act as a bridge, helping patients through a critical period of shock, but ***they are not definitive therapy***. IABP contraindicated if aortic regurgitation is present or aortic dissection is suspected.

| | |
|---|---|
| **Acute Myocardial Infarction with Cardiogenic Shock**<br>↓<br>IABP followed by emergency CAG and revascularization by PCI or CABG<br>↓<br>(Thrombolytics when emergency PCI/CABG not available) | **Intra-aortic Balloon Counterpulsation**<br>An IABP reduces systolic afterload and augments diastolic perfusion pressure without an increase in oxygen demand. An IABP should be used for MI patients when cardiogenic shock is not quickly reversed with pharmacologic therapy. Use of an IABP in cardiogenic shock complicating acute MI improves survival and is recommended as a stabilizing measure before angiography and prompt revascularization in appropriatety selected patients. |

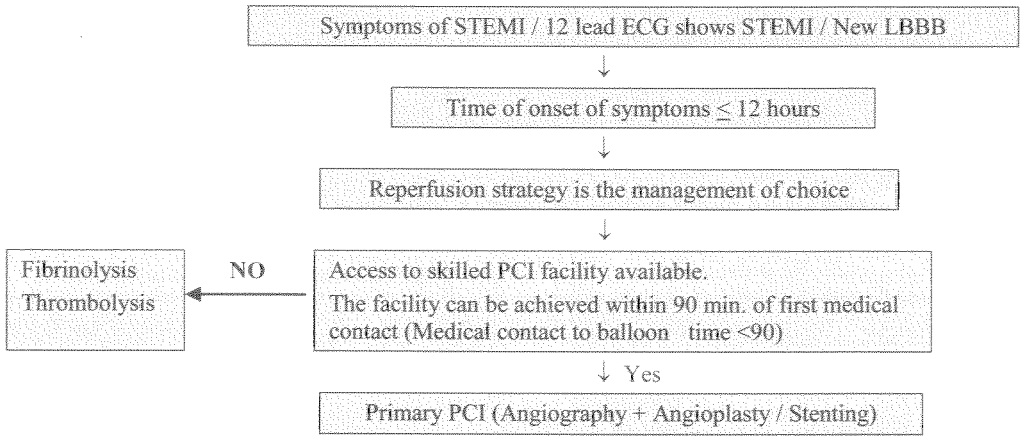
**267. Answer is a D (Primary angioplasty) :** Harrison 18th/p 2027 *Harrison 16th/1453, 1460; 17th/ 1537;CMDT 2006 / 38 360; CMDT 2009/314; ALS resusci-tation council UK 5th / 4*

*Immediate coronary angiography and primary percutaneous intervention (angioplasty stenting) is the treatment of choice for patient of ST elevation MI presenting within the first 12 hours of MI.*
The question does not provide us with sufficient information to determine best strategy of management. Presuming all favourable factors, primary percutaneous intervention with angiography and angioplasty is the single best answer of choice. ***IABPs act as a bridge stabilizing measure to help patients through a critical period of shock, but it is not a definitive therapy***

**Treatment of ST elevation Acute MI : Thrombolysis vs PCI**

- The current recommendation is to Treat with Reperfusion Therapy either primary percutaneous Coronary Intervention of Thrombolytic therapy.
- Immediate coronary angiography and primary PCI of the infarct related artery is shown to be superior to thrombolysis provided it is performed by experienced operators in high volume centres.
- Primary PCI is also the treatment of choice in patients with absolute and many relative contraindications to thrombolysis.
- In the subgroup of patients with Cardiogenic Shock Primary PCI is the preferred management.

***The patient in question has an acute anterior wall infarction along and is presenting with hypotension (? Cordiogenic shock). Angiography will primary PCI (Angiopathy) is the recommended / ideal immediate modality of treatment.***




**268. Answer is D (Streptokinase):** *Refer previous question*

***The patient is presenting as a case of Non ST Elevation MI (NSTEMI).***
***Thrombolytic therapy is reserved for patient with STEMI and is not indicated in NSTEMI.***

**269. Answer is A (Aspirin):** Harrison 18th/p 2025, 2029 *Harrison 17th/1535,1538; Hurst 12th/1378*

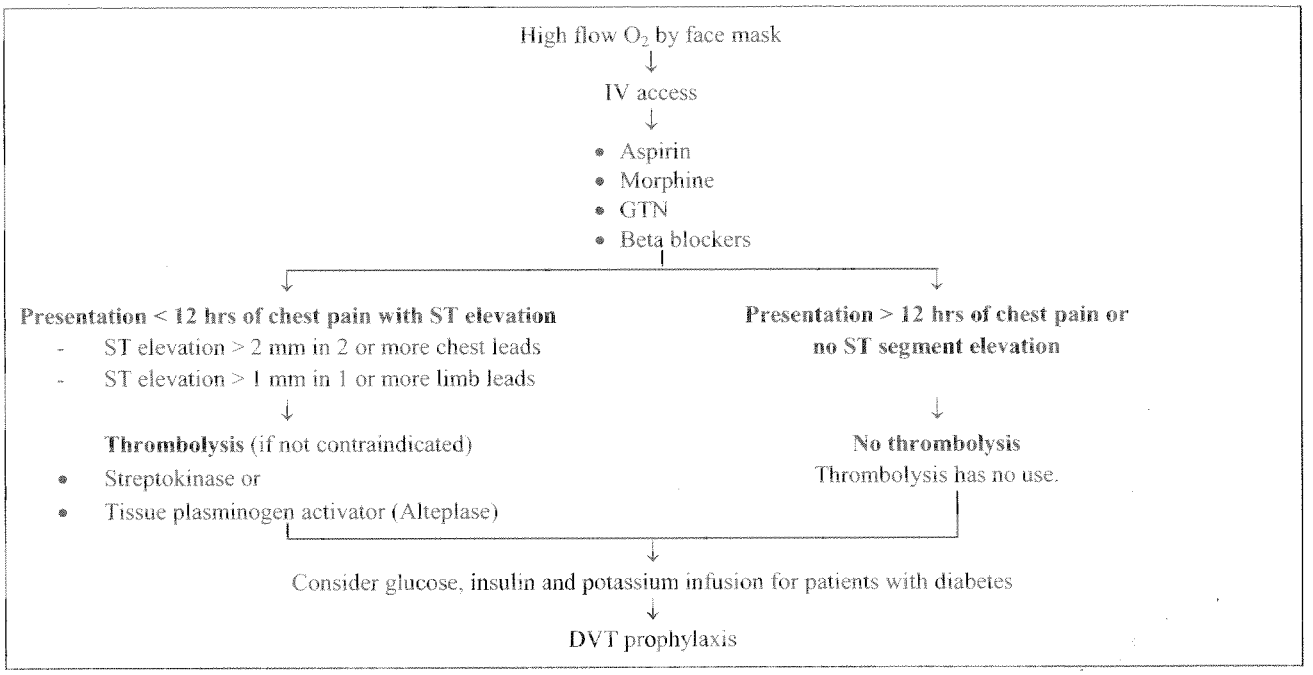
***Aspirin decreases mortality in myocardial infarction and should be administered as early as possible and in patients with Acute coronary syndromes including STEMI-Hurst***

***Althrough reperfusion therapy (Thrombolytic therapy) forms the main goal of management in STEMI, administration of Aspirin should not be delayed while patient is being assessed for suitability of thrombolysis. Aspirin has been shown to offer nearly as great an advanteage as that of streptokenose alone in certain trials. Aspirin should be administered as soon as a patient presents with any suspected Acute coronary syndrome including STEMI (As soon as possible)***

**270. Answer is D (Calcium channel blockers):** *Harrison 18th/p 2026; 17th/1536; CMDT 2004/ 344*

*'Results of multiple trials of different calcium antagonists have failed to establish a role for these agents in the treatment of most patients with MI, in contrast to the more consistent data that exist for other drugs eg. beta blockers, aspirin and fibrinolytic agents. The routine use of calcium channel blockers can not be recommended'*
*– Harrisons 16th/ 1455.*

**Management of acute MI**




**271. Answer is B (Plasminogen activator inhibitor):** *Harrison 17th/1536; CMDT 2008/317*

*Plaminogen Activators are used in MI and not inhibitors of Plasminogen activators.*
*The management of MI requires fibrinolysis, which is achieved by Plasminogen activators and not by Plasminogen inhibitor.*

**272. Answer is D (Warfarin):** Harrison 18th/p 2030 *Harrison 17th/1539; CMDT 2008/317, 318, 320*

*Warfarin is not indicated in the immediate management of Acute myocardial infarction.*
*Warfarin is the single best answer of exclusion.*

***Aspirin and Heparin*** *are used in early treatment of Acute Myocardial infarction to prevent thrombosis.*
**Alteplase or Tissue Plasminogen Activator** *is a thrombolystic agent and is indicated early in the treatment of STEMI.*

**273. Answer is A (Intracranial malignancy):** *Braunwald's 8th/1237*

***Malignant Intracranial Neoplasm is an absolute contraindication for Thrombolysis (Streptokinase / Urokinase).***

Contraindications and Cautions for Fibrinolytic Use in STEMI:

| Absolute Contraindications | Relative Contraindications |
|---|---|
| • Any prior intracranial hemorrhage<br>• Known structural cerebral vascular lesion (e.g., arteriovenous malformation)<br>• ***Known malignant intracranial neoplasm (primary or metastatic)***<br>• Ischemic stroke within 3 months (Except acute inschemic stroke within 3 hr.)<br>• Suspected aortic dissection<br>• Active bleeding diathesis (excluding menses)<br>• Significant closed head or facial trauma within 3 mo. | • History of chronic severe poorly controlled hypertension<br>• Severe uncontrolled hypertension on presentation (SBP > 180 Hg or DBP > 110 Hg)<br>• History of prior ischemic stroke > 3 months, dementia, or known intracranial pathology not covered in contraindications<br>• Traumatic or prolonged (>10 min) CPR or major surgery (<3 wk)<br>• Recent (within 2-4 week) internal bleeding<br>• Non compressible vascular punctures<br>• For streptokinase/anistreplase: prior exposure (>5 days ago) or prior allergic reaction to these agents<br>• Pregnancy<br>• Active peptic ulcer<br>• Current use of anticoagulants (the higher the INR, the higher the risk of bleeding) |

**274. Answer is A (Joint Pain):** Harrison 18th/p 2028 *KDT 6th/606; Harrison 17th/1538*

*Joint pain is not a recognized complication of streptokinase usage.*

Complication of streptokinase

- *Hypersensitivity reaction and Anaphylaxis (specially when used second time)*
- *Haemorrhage (Intracranial bleed: Risk of stroke)*
- *Fever*
- *Hypotensin*
- *Arrhythmia*

**275. Answer is D (Right Ventricular infarction):** *Harrison 15th/ 1396; 17th/154, CMDT 2003 page 356, 2005/ 352*

*"Right ventricular infraction presents as hypotension with relatively preserved left ventricular function and should be considered whenever patients with inferior infarction exhibit signs of low cardiac output and raised venous pressure (Shock)" – CMDT 2005/ 352*

*Patient in question fulfills the above criteria i.e., he presents in shock (hypotension) following inferior infarction and hence is most likely a candidate for right ventricular infarction.*

- **Right ventricular** infarction is present in one third of patients with inferior wall infarction and presentation is consistent with shock.
- Cardiac rupture (myocardial rupture): Complete rupture of the ventricular free wall occurs in less than 1% of patients and usually results in immediate death – CMDT 2005/ 353 *(Occurs 2-7 days post infarction)*
- Rupture of papillary muscle or of interventricular septum: Partial or complete rupture of a papillary muscle or of interventricular septum occurs in less than 1% of acute MI (both anterior and inferior MI)
  They are detected by appearance of new systolic murmur and clinical deterioration often with pulmonary edema.

**276. Answer is A (Fluids):** Harrison 18th/p 2032 *Harrison 17th/1541; Harrison pretest based on Q. 32 15th/e*

*The man in question has a right ventricular infarction as indicated by signs of low cardiac output and shock following an inferior MI. The fact that right atrial pressure is elevated out of proportion to left atrial pressure almost confirms the diagnosis. Therapy consists of volume expansion or fluid loading to maintain adequate RV preload.*

| | | |
|---|---|---|
| Pulmonary Artery pressure | 22/4 mmHg | Represent Right Atrial pressure |
| Pulmonary Capillary Wedge pressure | 4 mmHg | Represents Left Atrial pressure |

**Cardiac output is depressed due to an insufficient left heart filling pressure. The best treatment consists of administration of fluids.**

**277. Answer is A (I.V. fluids):** *Harrison 17th/1541; Harrison 18th/p 2031 CMDT 2005/ 352*

*Inferior wall MI suggests that the patient has right ventricular infarction.*

R.V. infarction should be considered whenever a patient with inferior wall infarction exhibits signs of low cardiac output and raised venous pressure with or without hypotension.

*Therapy essentially consists of volume expansion or fluid loading to maintain adequate R.V preload*, and efforts to improve left ventricular performance with a tendent reduction in PCWP and pulmonary arterial pressure.

**278. Answer is C (Right Ventricular infarction):** Harrison 18th/p 2031 *Harrison 17th/1541; CMDT 2005/352; Repeat*

*'Right ventricular infarction should be considered whenever a patient with inferior infarction exhibits signs of low cardiac output and raised venous pressure' – CMDT*

*Mitral regurgitation, decreased ejection fraction and septal defect are features of anterior wall MI.*

**279. Answer is B (Mitral regurgitation):** *Harrison 14th/ 1362; Harrison 15th/ 1396; Harrison 16th/ 1450; 17th/ 1533*
Harrison 18th/p 2022

*The most common valvular lesion seen in MI is mitral regurgitation.*

*The reported incidence of these murmurs of MR during first few days of onset of MI varies widely from 10 to 50 percent of patients – Harrison 14th*

- Dysfunction of mitral valve apparatus with a transient midsystolic or late systolic apical systolic murmur (regurgitant murmur) may be present as part of the physical findings of MI – Harrison 16th/7
- The most common cause of MR following MI is dysfunction of mitral valve due to ischaemia or infarction.

**280. Answer is D (External cardiac rupture):** *Harrison 14th/1362; 15th/1396; 16th/not elaborated in text. 17th/1491, 1492*

*Typical symptoms of sudden decrease in B.P. and electromechanical disassociation seen in the first week of M.I., point to the diagnosis of External cardiac rupture.*

| Risk factors | Clinical presentation |
|---|---|
| 1. Increasing age<br>2. History of hypertension<br>3. First infraction<br>4. No history of angina<br>5. Large Q wave infarct<br>6. Presentation during first week following MI. | Sudden loss of pulse. BP consciousness while ECG continues to show sinus rhythm i.e. ***electromechanical dissociation.*** |

*The patient in question fulfills most diagnostic features leading us to a diagnosis of Myocardial free wall rupture.*

**281. Answer is A (Complete heart block):** *CMDT 2008/323; 'Cardiology Secrets 2nd/113*

*Complete heart block is not a cause for new onset systolic murmur after Acute Myocardial Infarction.*

Cause of new systolic murmur after Acute Myocardial infarction

- *Papillary muscle dysfunction/rupture (causing severe mitral regurgitation)*
- *Rupture of interventricular septum*
- *Right ventricular infarction and tricuspid regurgitation*
- *Free wall rupture*
- *Left ventricular outflow tract obstruction*

Note:
***Ischemic cardiomyopathy*** *is defined as dilated cardiomyopathy in a subject with history of MI. This may lead to papillary muscle dysfunction and hence produce a new onset systolic murmur.*

**282. Answer is A (Occurs with in hours after myocardial infarction):** D. Responds well to salicylates *Robbin's illustrated 7th/ 557*

*Dressler's syndrome develops after an interval of 1 to 4 weeks (or even month) following cardiac injury (MI) and not within hours.*

Dressler's syndrome / Post Cardiac Injury Syndrome

- *Dressler's syndrome refers to a delayed form of autoimmune pericarditis that develops weeks after myocardial infarction*

  ***The pericarditis typically develops 1 to 4 weeks following cardiac injury / MI but may appear after several months. Recurrence may be seen sometimes upto 2 years or more after MI / Injury***

- *The mechanism is not certain but they are believed to result from a hypersensitivity reaction in which the antigen originates from the injured myocardial tissue.*

  *Autoimmune mechanism; Circulating antibodies to myocardium occur frequently.*

- *Dressler's Syndrome is typically characterized by polyserositis including pericarditis and pleuritis*

  - Inflammation associated with Dressler's syndrome may result in the accumulation of fluids within the pericardium (pericardial effusion).
  - The immune system response that leads to Dressler's syndrome may also contribute to Pleurisy and/or Pleural effusion

- *Pathological pericarditis may be of the fibrinous variety*
- ***The principal symptom is 'chest pain' of acute pericarditis/pleuritis***
- *Leukocytosis, ↑ESR and ECG changes of acute Pericarditis may also occur.*
- ***The pericarditis is usually resolves in 1 to 2 weeks with aspirin, NSAIDS or analgesics (often no treatment is necessary)***
- ***Therepy with corticosteroids may be required in resistant cases***

**283. Answer is D (Treatment with steroids is necessary):** *Harrison's 18th/1974; Braunwald 10th/1653*

*Treatment with steroids is not necessary in patients with Dressler' syndrome.*

**284. Answer is B (Thallium scan):** Harrison 18th/p 2024 *Harrison 17th/1534, Pathophysiology of Heart Disease br 'Lilly' 4th/68*

***Reversible Myocardial Ischemia can be detected by myocardial perfusion imaging using compounds labeled with thallium- 201 (Thallium Scan)***

**What is Reversible Myocardial Ischemia: Role of Thallium scanning**

- Reversible myocardial ischemia refers to areas of myocardium that become ischemic on stress /exercise, but region viability / circulation on resting and do not progress to infarction
- Such areas of myocardium can be detected by myocardial perfusion imaging using the Thallium scan.
- Thallium scan can thus help in distinguishing between on ischemic area (reversible) and an infracted / scarred area of myocardium (irreversible)

**Thallium Scanning**

Thallium ~201 ($T_1^{201}$) is injected intravenously while patient is exercising on Trade mill or stationary bicycle.

- Thallium enters myocytes depending on vascular supply (perfusion) and membrane function (tissue viability)
- The intracellular concentration of thallium is estimated by the density of image

**Normal Myocardium**

Shows homogeneous distribution of thallium in the myocardial tissue and appears dark on the scan

**Ischemic / Infracted (scarved) Myocardium**

Do not accumulate as much thallium as normal myocardium and appear as 'light' or 'cold spots' on the scan.

Thallium accumulation does not remain fixed in myocytes. Rather continuous redistribution of the isotope occurs across the cell membrane over time, and after few hours all viable myocytes accumulate more isotope and redistribution causes all viable myocytes to have equal concentration of $T_1^{201}$

To differentiate between reversible myocardial ischemia and irreversible myocardial ischemia (infarction) another set of images are taken when patient is resting (acquired after several hours)

**Delayed Thallium Scan (After 3-4 hours) (Redistribution Imaging)**

**Reversible Ischemia**

Defects seen on initial films that have resolved suggest Reversible ischemia (cold spot disappears)

**Irreversible Ischemia (Infarction / scarring**

Defects seen on initial film that persist as cold spots suggest irreversible ischemia or infracted /scarred myocardium

**285. Answer is C (Thallium scan):** Harrison 18th/p 2024 *Harrison 15th/ 1276; Harrison 16th/ 1324; Harrison 17th/ 1534; Refer previous question*

***Reversible Myocardial Ischemia can be detected by myocardial perfusion imaging using compounds labeled with thallium- 201 (Thallium Scan).***

**286. Answer is A (Rofecoxib):** *Harrison 18th/47; Goodman & Gillman 12th/974; 'Drug-Induced Diseases' 2nd/406*

***Rofecoxib (selective COX-2 inhibitor) induces a Prothrombotic state and has been linked to increased incidence of thrombotic events including myocardial infarction, stroke and venous thrombosis.***

'*Selective COX-2 inhibitor Rofecoxib increases the risk of myocardial infarctions*' – Harrison 18th/47

'*Placebo controlled trials with three structurally distinct COX-2 inhibitors – Celecoxib, valdecoxib (withdrawn) and rofecoxib (withdrawn) revealed an increase in the incidence of myocardial infarction, stroke and thrombosis*'.

*– Goodman & Gillman 12th/974*

Rofecoxib and Valdecoxib were withdrawn from the market in 2004 and 2005 respectively due to increased risk of thrombogenic cardiovascular events (myocardial infarction, stroke and thrombosis)

**Mechanisms of Drug-Induced Myocardial Ischemia and Acute Coronary Syndrome**

| Mechanism | Examples |
|---|---|
| **Increased Myocardial Oxygen Demand** | |
| • Increased heart rate | Directly: Cocaine, adrenergic adrenergic β-agonists, sympathomimetics, withdrawal of β-antagonists<br>Indirectly: potent vasodilators (Nifedipine, minoxidil, hydralazine) |
| • Increased myocardial contractility | Directly: Cocaine, adrenergic β-agonist, sympathomimetics, withdrawal of β-antagonists<br>Indirectly: potent vasodilators (Nifedipine, minoxidil, hydralazine) |
| • Increased left ventricular systolic wall tension | Cocaine, phenylephrine |
| **Decreased Myocardial Oxygen Supply (temporary, non-total occlusion)** | |
| • Increased coronary vascular resistance (vasospasm, thrombosis) | Cocaine, anti-migraine agents (ergot alkaloids, triptans) |
| • Decreased coronary diastolic perfusion pressure | Enalapril, nifedipine, minoxidil, hydralazine, nitroprusside, adenosine, dipyridamole |
| **Drug-Induced Acute Coronary Syndromes** | |
| • **Acute coronary syndrome associated with acute drug therapy**<br>- Coronary artery thrombosis, superimposed on a damaged atherosclerotic plaque<br>- Coronary artery vasospasm (with or without a superimposed coronary artery thrombosis) | Cocaine, oral contraceptives, estrogens, ***COX-2 inhibitors***, NSAIDs<br>Cocaine, anti-migraine agent (ergot alkaloids, triptans) |
| • **Acute coronary syndrome associated with chronic drug therapy** (Increased cardiovascular risk) | Cocaine, estrogens, ***COX-2 inhibitors***, NSAIDs, HIV agents/protease inhibitors, oral contraceptives, rosiglitazone |

**287. Answer is B (Left ventricular ejection fraction):** *Harrison 18th/p 2024, 2031, 2034; 17th/ 1534, 1535, 1540, 1543*

*Pump failure is now the primary cause of in hospital death following MI. The degree of pump failure relates well with mortality.*

*The most sensitive index of cardiac function amongst the options provided is 'ejection fraction' i.e. the ratio of stroke volume to end diastolic volume. This is thus the best indicator of mortality & morbidity following MI.*

## Cardiomyopathy/HOCM

**288. Answer is D (Alkaptonuria):** *Harrison 16th /1408; Harrison 17th/1481 (table 231-1); 1410; Harrison 18th/ 1959, 1965*

***Friedreich's ataxia, Glycogen storage diseases and Muscular dystrophies are known to cause of cardiomyopathy. Alkaptonuria has not been mentioned to cause cardiomyopathy.***

| **Primary myocardial involvement** | |
|---|---|
| Idiopathic (D,R,H)<br>Failmilial (D,R,H)<br>Eosinophilic endomyocardial disease (R)<br>Endomyocardial fibrosis (R) | |
| **Secondary Myocardial involvement** | |
| *Infective (D)*<br>• Viral myocarditis<br>• Bacterial myocarditis<br>• Fungal myocarditis | *Connective tissue disorder (D)*<br>• Systemic lupus erythematosus<br>• Polyarteritis nodosa<br>• Rheumatoid arthritis |

| | |
|---|---|
| • PRotozoal myocarditis<br>• Metazoal myocarditis<br>• Spirochetal<br>• Rickettsial<br>*Metabolic (D)*<br>*Familial storage disease (D,R)*<br>• ***Glycogen storage disease***<br>• Mucopolysaccharidoses<br>• Hemochromatosis<br>• Fabry's disease<br>*Deficiency (D)*<br>• Electrolytes<br>• Nutritional | • Progressive systemic sclerosis<br>• Dermatomyositis<br>*Infiltratiions and granulomas (R,D)*<br>• Amyloidosis<br>• Sarcoidosis<br>• Malignancy<br>*Neuromuscular (D)*<br>• ***Muscular dystrophy***<br>• Myotonic dystrophy<br>• ***Friedreich's ataxia (H,D)***<br>*Sensitivity and toxic reactions (D)*<br>• Alcohol<br>• Radiation<br>• Drugs<br>*Peripartum heart disease (D)* |



**289. Answer is A (Dilated cardiomyopathy):** *Harrison 18th /1952*

***Contractile dysfunction (systolic failure) is the dominant feature of dilated cardiomyopathy.***

*'An enlarged left ventricle with decreased systolic function (contractile dysfunction) as measured by left ventricular ejection fraction charachterizes diated cardiomyopathy. Systolic failure is more marked than the frequently accompanying diastolic dysfunction'- Harrison's 18th/ 1952*

**290. Answer is A (Dilated Cardiomyopathy):** *API Textbook of Meidicne 9th/ 728*

*Dilated Cardiomyopathy (DCM) is the most common type of cardiomyopathy in India and the western world.*

*'Dilated Cardiomyopathy (DCM) is the most common type of cardiomyopathy' – API Textbook of Medicine 9th/ 728*

| |
|---|
| *Note :*<br>*The most common cause of dilated cardiomyopathy is Idiopathic (Two-Thirds)*<br>*The most common toxin implicated in chronic dilated cardiomyopathy is Alcohol* |

**291. Answer is A (Alcohol):** *Harrison 18th/ 1961*

*Chronic Alcohol Consumption is the most common cause of Toxic Dilated Cardiomyopathy.*

*'Alcohol is the most common toxin implicated in chronic dilated cardiomyopathy' – Harrison 18th/1961*

| |
|---|
| *Note :*<br>*Dilated cardiomyopathy is the most common type of cardiomyopathy*<br>*The most common cause of dilated cardiomyopathy is Idiopathic (Two-Thirds)*<br>*Alcohol Consumption is the most common cause of Toxic Dilated Cardiomyopathy* |

**292. Answer is A (Dilated Cardiomyopathy):** *Harrison's 18th/ 1964*

*Tako-Tsubo cardiomyopathy is a rare form of dilated cardiomyopathy.*
*Tako-Tsubo cardiomyopathy also known as stress cardiomyopathy, apical ballooning syndrome or 'Broken Heart Syndrome' is a type of dilated cardiomyopathy seen predominately in older women (usually over the age of 50 years) after sudden intense emotional or physical stress. It is thought to be caused by the release of catecholamines (adrenergic surge) from severe physical and/or emotional stress. The ventricle shows global ventricular dilation with basal contraction forming the shape of a narrow necked jar called 'Taka-Tsubo' which is used in Japan to trap octopi. In the majority of cases all the symptoms are resolved in 3to 7 days without any residual effects.*

**293. Answer is C (Amyloidosis):** *Harrison 18th/p 1965 CMDT 2003 /395, 396; 2005/391; 2008/357*

*Although all options mentioned in the question other than alcohol have been listed as causes for restrictive cardiomyopathy, amyloidosis appears to be the commonest cause amongst them.*

- *'The most frequent causes of restrictive cardiomyopathy are amyloidosis, radiation and myocardial fibrosis fter open heart surgery' – CMDT 2005 / 391*

- 'Myocardial involvement with amyloid is a common cause of secondary restrictive cardiomyopathy' – *Harrison 16th/*

| **Causes include:** *(Harrison 16th/ 1412)* | |
|---|---|
| 1. Amyloidosis. | 6. Fabry's disease |
| 2. Hemochromatosis | 7. Eosinophilia |
| 3. Glycogen deposition | 8. Scleroderma |
| 4. Endomyocardial fibrosis | 9. Transplanted heart |
| 5. Sarcoidosis | 10. Mediastinal irradiation |
| | 11. Neoplastic irradiation |

**294. Answer is A (HOCM):** *Harrisons 16th /1410, 1411, API textbook of Medicine 8th/575*

***Syncope and sudden death following competitive sports in young individuals is characteristic of Hypertrophic Obstructive Cardiomyopathy (HOCM). The presence of Left ventricular Hypertrophy predominantly affecting the Septum, on autopsy confirms the suspected diagnosis of HOCM.***

*'Syncope and sudden death following competitive sports warrants early diagnosis of this condition in suspected families, Echocardiography should be done to screen their asymptomatic relatives' – API*
*'Left ventricular Hypertrophy predominantly affecting the septum and anterolateral wall is the diagnostic feature'- API*

**Distinctive Pathophysiological features include**

**Heterogeneous hypertrophy of LV**

| **Septal Hypertrophy** | **Dynamic LV outflow obstruction** |
|---|---|
| • Pattern of hypertrophy is distinctive<br>• ***Asymmetrical septal hypertrophy*** is characteristic<br>• Thickness of ventricular septum is disproportionately increased when compared with the free wall | • Dynamic LV outflow obstruction: it is related to narrowing of the subaortic area as a consequence of opposition of anterior mitral valve leaflet against the hypertrophied septum in midsystole. The concept is termed ***systolic anterior motion (SAM)*** of mitral valve.<br>• Dystolic dysfunction: The ubiquitous pathophysiological abnormality is not systolic but rather ***diastolic dysfunction*** - *Harrison* |

**Clinical spectrum of HOCM**

| **Asymptomatic patient** Q | **Sudden death** Q | **Symptomatic patient** |
|---|---|---|
| many patients are asymptomatic | Sudden death may be first clinical manifestation of disease (commonly seen in young adults after competitive sports) | |

| **Symptoms** | **Signs** | | |
|---|---|---|---|
| • Dyspnea Q is the commonest symptom<br>• Angina pectoris/chest pain Q<br>• Fatigue Q<br>• Syncope Q | • **Double or triple precardial impulse** Q<br>• **Brisk carotid upstroke** Q (Rapidly rising carotid pulse) | • **Fourth heart sound** Q | **Systolic murmur** (Hallmark of disease)<br>• Harsh Q<br>• Diamond shaped (crescendo decrescendo) Q<br>• Best heard at lower left sternal border as well as at apex Q |

**295. Answer is D (HOCM):** *Ferri's Clinical Advisor 2013 (Elsevier)/205*

***Hypertrophic Obstructive Cardiomyopathy (HOCM) is the most common cause of sudden death in young athletes***

***Aortic Stenosis is the most common valvular disease associated with sudden death***

**296. Answer is A. (HOCM):** *Harrison's 16th/1410-1411, API Textbook of medicine 8th/575; Harrison's 17th/1484-1485 Harrison 18th/ 1968, 1970*

***Sudden death following competitive sports in young individuals is characteristic of hypertrophic obstructive cardiomyopathy (HOCM). The presence of chamber and septal hypertrophy on autopsy confirms the suspected diagnosis of HOCM***

**297. Answer is A (β agonists are useful):** *Harrison 14th 15th/ 1351, 1343; 16th/ 1399; 17th/ 1485;* Harrison 18th/p 1969 *other references.*

***β-blockers should be used as the initial drug in symptomatic individuals. β- agonists are contraindicated.***

- Hypertrophic obstructive cardiomyopathy is characterized by hypertrophy of left ventricle in the absence of an obvious cause such as hypertension or aortic stenosis.

**Distinctive Pathophysiological features include:**

| Heterogeneous hypertrophy of LV | Dynamic LV outflow obstruction |
|---|---|
| • Pattern of hypertrophy is distinctive<br>• ***Asymmetrical septal hypertrophy*** is characteristic mainly affecting the IV septum and anterolateral wall<br>• Thickness of ventricular septum is disproportionately increased when compared with the free wall | • The LV outflow obstruction is dynamic i.e. it is related to narrowing of the subaortic area as a consequence of opposition of anterior mitral valve leaflet against the hypertrophied septum in midsystole. The concept is termed ***systolic anterior motion (SAM)*** of mitral valve. |

- The obstruction in HOCM is dynamic and is caused by the opposition of mitral valve leaflet against the hypertrophied septum during systole. Increase in volume of blood in LV will move the muscular obstruction away from the opposite wall and decrease the obstructing agent as well as the intensity of murmur. Passive leg raising augments venous return, increases the volume of blood in LV, decreases the obstruction and hence decreases the murmur.
- Increase in myocardial contractility worsens the obstruction by moving the opposing walls closer to each other. β agonists (increase myocardial contractility) would thus increase the obstruction and should not be used. β blockers on the other hand are the agent of choice as these decrease myocardial contractility and hence relieve the obstruction by moving the opposing walls away from each other.

**Remember**

*Clinical Features:*
- Most common complaint in symptomatic patient -- Dyspnoea. Q
- Sudden Death Q may be the first manifestation.
- The Hallmark of HOCM is a *systolic murmur* Q most often due to MR. Q
- Double - Triple Apical impulse may be seen. Q

*Diagnosis:* The mainstay of diagnosis is *Echocardiography* Q which demonstrates :
- Asymmetrical LV hypertrophy. Q
- Systolic anterior motion of mitral valve. Q

*Treatment:*
- **β blockers should be the initial drug** Q *in symptomatic* individuals.
- *$Ca^{++}$ channel blockers may be given.* Q

***Avoid*** Q :
- Digitalis Q
- Nitrates Q
- Diuretics Q
- β agonists Q

**298. Answer is B (Murmur radiating to neck):** *Harrison 16th/ 1411; Harrison 17th/ 1484, 1485*Harrison 18th/p 1968

***Hypertrophic cardiomyopathy is characterized by a harsh systolic diamond shaped (crescendo-decrescendo) murmur best heard at lower left sternal border as well as at apex. Murmur does not radiate to the neck. Other features mentioned are consistent with the diagnosis***

*Valsalva maneuver and sudden standing decrease the volume of blood in LV and increase the obstruction by allowing better opposition between the hypertrophied septum of the mitral valve leaflet. Thus these will also increase the intensity of the murmur*

**299. Answer is D (Pathophysiological Systolic Dysfunction):** *Harrisons 16th /1410, 1411, API textbook of Medicine 8th/575*

***The ubiquitous pathophysiological abnormality in Hypertrophic Obstructive Cardiomyopathy (HOCM) is not systolic but rather diastolic dysfunction.***

*Hypertrophic Obstructive Cardiomyopathy (HOCM) characterized by* ***Asymmetrical Septal Hypertrophy*** and ***Dynamic Left Ventricular Outflow Obstruction.*** *Dynamic LV outflow obstruction* is related to narrowing of the subaortic area as a consequence of opposition of anterior mitral valve leaflet against the hypertrophied septum in mid-systole. The concept is termed ***Systolic Anterior Motion (SAM)*** of the mitral valve. *The ubiquitous pathophysiological abnormality in Hypertrophic Obstructive Cardiomyopathy (HOCM) is not systolic but rather* ***diastolic dysfunction***

**300. Answer is A (Systolic dysfunction):** *Harrison 16th/1410; Harrison 17th/ 1484; Harrison 18th/p 1968*

*'The ubiquitous pathophysiological abnormality in hypertrophic obstructive cardiomyopathy is not systolic but rather diastolic dysfunction' – Harrisons*

*Note: It has now been demonstrated that systolic dysfunction characterized by an outflow tract pressure gradient is present only in about one quarter of patients with HCM. The pathophysiological abnormality that has now been demonstrated is diastolic dysfunction characterized by increased stiffness of the hypertrophied muscle.*

**301. Answer is A (Supine position):** *Harrison 15th/ 1362, Harrison 16th/ 1411; Harrison 17th/ 1484; Harrison 18th/p 1968*

| Condition which increase obstruction & intensity of murmur | Conditions which decrease obstruction & intensity of murmur |
|---|---|
| **Factors that increase myocardial contractility** | **Factors that decrease myocardial contractility** |
| • *Exercise*[Q] | • β blockers |
| • *Sympathomimetic Amines*[Q] | • calcium channel blockers |
| • *Digitalis Glycosides*[Q] | **Factors which increase Ventricular volume** |
| **Factors which decrease Ventricular volume** | • *Augmentation of venous return by passive leg raising*[Q] |
| • *Valsalva maneuver*[Q] | • *Expansion of Blood Volume*[Q] |
| • *Sudden standing*[Q] | • *Supine* ***Position***[Q] |
| • *Nitroglycerine*[Q] | **Increased aortic impedance & afterload:** |
| • *Amyl nitrite*[Q] | • *Elevation of Arterial pressure by phenylephrine*[Q] |
| • *Tachycardia*[Q] | • *Sustained hand grip*[Q] |
| **Decreased aortic impedance & afterload:** | • *Squatting* |

**302. Answer is B (Decrease of murmur with handgrip):** *Harrison 15th/ 1361 & 1362, Harrison 16th/ 1411; Harrison 17th/ 1484;* Harrison 18th/p 1968 *(Q.No 36 C.V.S Harrison pretest for medicine, 15/e)*

*The murmur decreases with increase in ventricular volume during isometric exercise (handgrip)*

*Echocardiographic evidence of disproportionately thickened ventricular septum and systolic anterior motion (SAM) of mitral valve strongly suggests Idiopathic hypertrophic Subaortic stenosis.* ***The Typical harsh systolic murmur does not radiate to carotid arteries and decreases with increase in ventricular volume during isometric exercise (handgrip).***

*Congestive heart failure often occurs because of reduced ventricular compliance despite normal ventricular systolic function. The carotid upstroke is brisk and often bifid.*

**303. Answer is C (Digoxin):** *Harrison 17th /1764; Harrison's 18th/2312*

*Digitalis is contraindicated in hypertrophic obstructive cardiomyopathy (HOCM).*

*Digitalis causes an increase in myocardial contractility, which increases the degree of obstruction in HOCM and worsens the condition.*

**Drugs Contraindicated in HOCM are**

| Drugs that increase myocardial Contractility | Drugs which decrease ventricular volume (preload) |
|---|---|
| • *Digitalis* [Q] | • *Nitrates* [Q] |
| • *Sympathomimetic amines* [Q] | • *Diuretics* [Q] |
| • *β agonist* | |

*Any increase in myocardial contractility or decrease in ventricular volume (preload) increase the degree of obstruction in HOCM*[Q]

**304. Answer is C (Propranolol):** *Harrison 15th/ 1361, Harrison 16th/ 1410; Harrison 17th/ 1485* Harrison 18th/p 1969, 1970

*The symptoms of the patient and echocardiographic finding of asymmetrical septal hypertrophy almost confirms the diagnosis of Hypertrophic cardiomyopathy. Beta Blockers should be the initial drug [Q] in symptomatic individuals*

**Management of HOCM**

- Avoidance of strenuous physical activity
- **Beta Blockers** should be the initial drug [Q] in symptomatic individuals. They reduce:
  - *Heart rate*
  - *Blood pressure*
  - *Stiffness of left ventricle*
  - *Fatal arrythmias*
- **Calcium channel Blockers**[Q] (verapamil and diltiazem) are alternative drugs.
  - They reduce-stiffness of ventricle
  - Elevated diastolic pressures
- **Amiadarone** may be used to reduce arrythmias.
- **Surgical myomectomy**

**305. Answer is D (Idiopathic Hypertrophic Sub Aortic Stenosis):** *Harrison 17th/ 1484, 1485; 18th/p 1968, 1969, 1970*

**Idiopathic hypertrophic subaortic stenosis** (HOCM) is a dynamic outflow obstruction which is increased by any mechanism decreasing the preload. *Nitrates decrease the preload, & the volume of blood in LV & thereby increase the dynamic obstruction & symptoms of angina.*

**306. Answer is B (Hypertrophic obstructive cardiomyopathy):** *Harrison / 1484, 1485* Harrison 18th/p 1968-1970

*Family history of the disease and aggravation of symptoms with the intake of Nitroglycerine (Nitrates) sugget the diagnosis of Hypertrophic obstructive cardiomyopathy.*

**307. Answer is A (Digitalis is useful):** *Harrison 17th/ 1485; Repeat*

*Digitalis is contraindicated in hypertrophic obstructive cardiomyopathy (HOCM).*

*Digitalis causes an increase in myocardial contractility which increases the degree of obstruction in HOCM and worsens the condition.*

**Drugs Contraindicated in HOCM are**

| Drugs that increase myocardial Contractility | Drugs which decrease ventricular volume (preload) |
|---|---|
| • *Digitalis* [Q] | • *Nitrates* [Q] |
| • *Sympathomimetic amines* [Q] | • *Diuretics* [Q] |
| • *β agonist* | |

*Any increase in myocardial contractility or decrease in ventricular volume (preload) increase the degree of obstruction in HOCM*[Q]

## Pericardial Disease

### Cardiac Tamponade

**308. Answer is D (Kussmaul's sign):** *Harrison 17th/ 1490, 1491; Harrison 18th/p 1975; Repeat*

*Pulsus paradoxus clinically, electrical alternans on ECG and RVDC on Echocardiography are chracteristic features of Cardiac tamponade.*

***A positive Kussmaul's sign is rare in cardiac tamponade. Its presence suggests that an organizing process and epicardial constriction are present in addition to effusion'*** *– Harrisons*

| Characteristic | Tamponade | Constrictive Pericarditis | Restrictive Cardiomyopathy | RVMI |
|---|---|---|---|---|
| *Clinical* | | | | |
| **Pulsus paradoxus** | **Common** | **Usually absent** | **Rare** | **Rare** |
| Jugular veins | | | | |
| Prominent y descent | Absent | Usually present | Rare | Rare |
| Prominent x descent | Present | Usually present | Present | Rare |
| **Kussmaul's sign** | **Absent** (Rare)$^{Q}$ | **Present** | **Present** | **Present** |
| Third heart sound | Absent | Absent | Rare | May be present |
| Pericardial knock | Absent | Often present | Absent | Absent |
| *Electrocardiogram* | | | | |
| Low ECG voltage | May be present | May be present | May be present | Absent |
| **Electrical alternans** | **May be present** | **Absent** | **Absent** | **Absent** |
| *Echocardiography* | | | | |
| Thickened pericardium | Absent | Present | Absent | Absent |
| Pericardial calcification | Absent | Often present | Absent | Absent |
| Pericardial effusion | Present | Absent | Absent | Absent |
| RV size | Usually small | Usually normal | Usually normal | Enlarged |
| Myocardial thickness | Normal | Normal | Usually increased | Normal |
| **Right atrial collapse and RVDC** | **Present** | **Absent** | **Absent** | **Absent** |
| Increased early filling, ↑ mitral flow velocity | Absent | Present | Present | May be present |
| Exaggerated respiratory variation in flow velocity | Present | Present | Absent | Absent |
| *CT/MRI* | | | | |
| Thickened/calcific pericardium | Absent | Present | Absent | Absent |
| *Cardiac catheterization* | Usually present | Usually present | Usually absent | Absent or present |
| Equalization of diastolic procedures | | | | |
| Cardiac biopsy helpful? | No | No | Sometimes | No |

*RV, right ventricle; RVMI, right ventricular myocardial infarction; RVDC, right ventricular diastolic collapse; ECG, electrocardiograph.

**Note:**

*'A positive Kussmaul's sign is rare in cardiac tamponade. Its presence suggests that an organizing process and epicardial constriction are present in addition to effusion' – Harrisons 16th/ 1416

**309. Answer is A (Kussmaul's sign):** *Harrison 16th/1416; Harrison 17th/ 1490, 1491; Repeat* Harrison 18th/p 1975

*Pulsus paradoxus clinically, electrical alternans on ECG and RVDC on Echocardiography are characteristic features of Cardiac tamponade.*

**310. Answer is C (Rapid y descent):** *Harrison 15th/ 1357, Harrison 16th/ 1416; Harrison 17th/ 1490* Harrison 18th/p 1972

*Cardiac tamponade is characterized by elevation of JVP with a prominent x descent and a diminutive or absent 'y' descent – Harrison 16th/ 1416*

*Rapid 'y' descent is seen in constrictive pericarditis.*

**Kussumaul sign** is a feature of constrictive pericarditis and not cardiac tamponade. It can however be seen (rare) in tamponade. *Its presence suggests that an organizing process and epicardial constriction are present in addition to effusion – Harrison 16th/ 1416*

| Clinical | Tamponade | Constrictive Pericarditis |
|---|---|---|
| • Pulsus parodoxus$^{Q}$ | **Common** | Usually absent |
| • Jugular veins | | |
| - Raised JVP | Present | Present |
| - *Prominent Y descent*$^{Q}$ | **Absent** | Usually Present |
| - *Prominent X descent*$^{Q}$ | Present | Usually present |
| • Kussumaul's sign$^{Q}$ | **Absent (Rare)** | Present |

**311. Answer is B (Cardiac Tamponade):** Harrison 18th/p 1975 *Harrisons 17th/1491, Hurst 12th/246,1966*

*Pulsus Paradoxus is most characteristic of cardiac tamponade amongst the options provided.*

| Feature | Cardiac Tamponade | Constrictive Pericarditis | Restrictive Cardiomyopathy | RVMI |
|---|---|---|---|---|
| Pulsus paradoxus | Common | Usually Absent | Rare | Rare |

*Pulsus Paradoxus is much more common with cardiac tamponade than with constrictive pericarditis of paradoxical pulse is considered more characterstic of cardiac tamponade than constrictive pericarditis.*
*Presence of paradoxical pulse is however not a specific feature of cardiac tamponade*

**312. Answer is B (Cardiac Tamponade):** Harrison 18th/p 1972 *Harrison's 17th/1490*

***Beck's triad is a feature of cardiac tamponade.***

**Beck's triad of Cardiac tamponade**

- *Hypotension*[Q]
- *Soft or Absent Heart Sounds*[Q]
- *Jugular venous distension*[Q] *(↑JVP with a prominent x descent but absent y descent)*

**313. Answer is D (Tachycardia):** Harrison 18th/p 1972 *Harrisons 17th/1490*

*The three principle features of Beck's triad are hypotension, soft or absent heart sounds and increased JVP*

Beck's Triad of Cardiac Tamponade

- *Hypotension*[Q]
- *Soft or absent Heart sounds (Silent Heart)* [Q]
- *Increased JVP (with a prominent x descent but absent y descent)*[Q]

**314. Answer is C (Muffled heart sound, distended neck veins, hypotension) : Repeat**

*The three principle features of Beck's triad are hypotension, muffled or absent heart sounds and distended neck veins (increased JVP)*

Beck's Triad of Cardiac Tamponade

- *Hypotension*[Q]
- *Soft or absent Heart sounds (Muffled Heart Sounds; Silent Heart)* [Q]
- *Increased JVP/ Distended Neck Veins (with a prominent x descent but absent y descent)*[Q]

**315. Answer is A, B, D:** Harrison 18th/p 1972 *Harrisons 17th/1490*

*The principle features of Beck's triad are Hypotension, Reduced or Absent Heart sounds (Silent Heart) and elevated JVP (Neck vein distension)*

**316. Answer is C (Cardiac Temponade):** *Harrison 14th/ 1336, 15th/ 1367, 16th / 1416; Harrison 17th/ 1490, 1491 Harrison 18th/p 1975, 1972*

*Cardiac Tamponade should be suspected in any patient who has a rapid down hill course and exhibits the features of rising venous pressure and falling arterial pressure following blunt injury to the chest.*

***The triad of cardiac tamponade :***

1. Rising systemic venous pressure
2. Falling Arterial pressure
3. Quiet heart (distant heart sounds)

We are often given a set of findings and asked to distinguish between cardiac temponade and constrictive pericarditis. Few guidelines to answer these kind of questions :

**Guidelines:**

| If the question talks about any of the following, mark your answer as 'Cardiac Temponade' | If the question talks about any of these, mark your answer as 'Constrictive Pericarditis'. |
|---|---|
| a. Elevated J.V.P. with a ***prominent x-descent*** (y-descent is diminutive or negative) | a. Elevated J.V.P. with a ***prominent y-descent*** (along with a prominent x-descent) |
| b. ***Electrical Alternans*** | ***b. Kussumaul's sign***, which is rare in cardiac temponade |
| c. ***Pulses paradoxus:*** *Hallmark of cardiac Temponade.* | ***c. Pericardial knock***, which is rare in cardiac temponade |

**317. Answer is B (Urgent pericardial tap):** *Harrison 15th/ 1367, 1368, 1369; Harrison 17th/ 1490, 1491, 1492 Harrison 18th/p 1972, 1974*

***'If manifestations of pericardial tamponade appear pericardiocentesis must be carried out at once; since relief of intrapericardial pressure may be life saving'*** *– Harrison 16th/ 1417*

- This patient is a case of acute tamponade as seen after cardiac trauma as suggested by the classical findings of :
  - *Falling arterial pressure*
  - *Increased venous pressure and*
  - *Faint heart sounds*

***In case of tamponade pericardiocentesis (pericardial tap) should be carried out at once, as the release of intrapericardial pressure is life saving.***

- Rapid **blood transfusion** though essential will be effective only once pericardial tap decompresses the pericardium and enables the heart to pump normally.
- **Intercostal tube drainage** is not indicated as air entry is adequate in both lung fileds.
- **Fixation of femur and repair of femoral artery** is not the immediate priority. Weak femoral pulsation may be a manifestation of falling arterial pressure due to cardiac tamponade and need to be explored only if patient fails to improve after pericardial tap and blood transfusion.

**318. Answer is D (Cardiac tamponade):** *Harrison 15th/ 1364, Harrison 16th/ 1416; 17th/ 1490* Harrison 18th/p 1972

***Features of rising pressure, falling arterial pressure and pulsus paradoxus following surgery on the heart leads us to the diagnosis of cardiac tamponade.***

**319. Answer is C (Cardiac tamponade) most probably:** *Harrison 16th/1416; Harrison 17th/1490, 1491;* Harrison 18th/p 1975 *Braunwald 8th/130*

***Kussmaul's sign is absent in cardiac tamponade.***

*Presence of Kussmaul's sign in cardiac tamponade suggests an organizing process and presence of epicardial constriction (constrictive pericarditis) in addition to effusion.* ***Kussmaul's sign is not a feature of isolated cardiac tamponade.***

Causes of Kussmaul's Sign (Braunwald)

| Classical Cause | Other Reported causes |
|---|---|
| ***Constrictive pericarditis*** | • *Right ventricular infarction (RVMI)*<br>• *Restrictive cardiomyopathy (RCMP)*<br>• *Pulmonary Embolism*<br>• *Advanced Systolic Heart Failure* |

**Kussmaul's sign is absent inisolated cardiac tamponade**

- *It is frequent with constrictive pericarditis and R.V.M.I.*
- *Not so frequent in R.C.M.P. but definitely present*
- *Rare (absent) in Cardiac Tamponade*

**320. Answer is C (Constrictive pericarditis):** *Harrison 18th/ 1975; Evidence-based Physical Diagnosis by Steven R. McGee (Elsevier Health Sciences, 2012)/ 301; Braunwald 8th/130*

*Kussmaul's sign is classically described in association with Constrictive Pericarditis.*

*Kussmaul's sign refers to paradoxical elevation of JVP/CVP during inspiration (In healthy persons venous pressure falls during inspiration because pressures in the right heart decrease as intrathoracic pressures fall)* ***The Kussmaul's sign is classically described in association with Constrictive pericarditis****. Kussmaul's sign is however also seen in association with Right Ventricular Infarction, Restrictive Cardiomyopathy, Pulmonary Embolism and Advanced Systolic Severe Heart Failure*

**321. Answer is B (Pericardial Tamponade):** *Harrison 18th / 1975; Braunwald 8th/130*

*Kussmaul's sign is absent/rare in Cardiac Tamponade.*
*Presence of Kussmaul's sign in cardiac tamponade suggests an organizing process and presence of epicardial constriction (constrictive pericarditis) in addition to effusion.* ***Kussmaul's sign is not a feature of isolated cardiac tamponade.***

| *Feature* | *Tamponade* | *Constrictive Pericarditis* | *Restrictive Cardiomyopathy* | *RVMI* |
|---|---|---|---|---|
| ***Kussmaul's Sign*** | ***Absent*** | ***Present*** | ***Present*** | ***Present*** |

**Kussmaul's sign** *is frequent with constrictive pericarditis and R.V.M.I..* It is *Not so frequent in R.C.M.P. but definitely present.* It is *Rare (absent) in Cardiac Tamponade*

**322. Answer is B (Low ECG voltage):** Harrison 18th/p 1975 *Harrison 17th/1491*

*The patient is presenting with characteristic features of Cardiac Tamponade.*

*'Low ECG voltage' is a feature of cardiac tamponade and the single best answer of choice amongst the options provided.*

**Presence of raised JVP and inspiratory decline in systolic arterial pressure of > 10mm Hg suggests a diagnosis of acute tamponade.**
*An important clue to the diagnosis of cardiac tamponade is the presence of greater than nonrmal (10mm Hg) inspiratory decline in systolic arterial pressure – Harrison 17th/1491*

**Kussmaul's sign, prominent y descent and thickened pericardium are not seen in cardiac tamponade.**

| Features | Cardiac Tamponade |
|---|---|
| *Kussmaul's sign* | *Absent* |
| *Prominent y descent* | *Absent* |
| *Thickened Pericardium* | *Absent* |
| *Low ECG voltage* | *May be present* |

**323. Answer is A (Pericardial Effusion):** *Sapira's Art and Science of Bedside Diagnosis (Lippincott Williams & Wilkins) 4th/362*

***Auenbrugger's sign is seen in Pericardial Effusion.***
*Auenbrugger's sign refers to bulging of the epigastrium that may be seen in cases of severe pericardial effusion.*

**Eponymous signs described in Pericardial Effusion**

| Sign | Presentation |
|---|---|
| *Friedreich's sign* | Sudden collapse in the distended neck veins with diastole suggests pericardial tamponade |
| *Pitres' sign* | Anterior bulging of the lower sternum suggests pericardial effusion |
| *Auenbrugger's sign* | Protuberance/Bulging of the epigastrium suggests massive pericardial effusion (Sign on Inspection) |

| | |
|---|---|
| *Sansom's sign* | Percussible dullness in the left third intercostal space suggests large pericardial effusion |
| *Greene's sign* | Lateral displacement of the percussed cardiac border with expiration suggests a large pericardial effusion |
| *Ebstein's sign* | A large pericardial effusion can blunt the percussible right cardiohepatic angle producing dullness along the lower right sternal border |
| *Rotch's sign* | Dullness at the right lower sternal border suggests large pericardial effusion |
| *Moschcowitz's sign* | In pericardial effusion, the transition on percussion from the lungs to the right heart border is abrupt |
| *Ewart's sign* | A large pericardial effusion produces egophony and bronchial breathing at the lower border of the left scapula |
| *Ewart's second sign* | A large pericardial effusion makes the first rib seem more prominent along the sternal border |
| *Dressler's sign* | Is dullness to percussion of the lower one half of the sternum<br>The Dressler sound is a flat sound on percussion the lower half or two third of the sternum. In the absence of mitral stenosis, this finding "should at once arouse suspicion of pericardial effusion". |
| *Bamberger's sign* | Dullness at the angle of the scapula that disappears when the patient leans forward is Bamberger's sign of pericardial effusion<br>*Dullness at the left lower lung field is Ewart's sign of pericardial effusion, while right-sided dullness is Conner's sign. Disappearance of Ewart's or Conner's signs when the patient sits up and leans forward is Bamberger's sign of pericardial effusion.* |

**324. Answer is B (Bunting of cardiophrenic angle on the right side):** *Sapira's Art and Science of Bedside Diagnosis (Lippincott Williams & Wilkins) 4th/ 362*

***Bunting of cardiophrenic angle on the right side (Cardiac Hepatic angle) represents the Ebstein sign of pericardial effusion. It is not part of Moschowitz triad in pericardial effusion.***

| **Moschcowitz Triad of Pericardial Effusion:** |
|---|
| • *Widening of the area of cardiac flatness to percussion (Widening of the cardiac silhouette)* |
| • *Widening or increase in cardiac dullness in the second intercostal space; and* |
| • *An abrupt transition of pulmonary resonance to cardiac dullness. (Normally there is a muffled area of epicardial fat evident on percussion of the right side of the heart that is lost in pericardial effusion).* |

**325. Answer is A (Sub-xiphoid):** *Cardiac Catheterization Handbook: Expert Consult by Kern (Elsevier Health Sciences, 2011)/302; Critical Care Medicine: Basic Science And Clinical Evidence(Springer, 2007)/ 827*

***Closed-needle pericardiocentesis via the sub-xiphoid is the preferred approach for removal and drainage of a pericardial effusion.*** *The sub-xiphoid approach is preferred, as one can aspirate fluid even in the case of small effusions. This route is extra-pleural and avoids the coronary, pericardial, and internal mammary arteries.*

| ***Approaches to Pericardiocentesis*** |
|---|
| 1. **Sub-xiphoid Approach**<br>(Preferred Approach as this route is extra-pleural and avoids the risk to coronary, pericardial, and internal mammary arteries) |
| 2. **Apical Approach**<br>(Used when the sub-xiphoid route is not successful or in patients with marked pulmonary hypertension) |
| 3. **Parasternal Approach**<br>(Left Fifth Intercostal Space and/or Right Fifth Intercostal Space may be utilized; Left Fifth Intercostal Space is utilized more commonly) |

**326. Answer is A (Left 5th Intercostal Space):** *API Textbook of Medicine (JP Medical Ltd) 2012/ 741*

*Left Fifth Intercostal Space is the most commonly utilized space for Parasternal Pericardiocentesis*

*'There are various sites for aspiration but the two commonest sites used are the sub-xiphoid and the left fifth intercostal space. The sub-xiphoid approach is the much preferred route, as one can aspirate fluid even in the case of small effusions. This route is extra-pleural and avoids the coronary, pericardial, and internal mammary arteries.*

*- API Textbook of Medicine*

**327. Answer is C (Visceral layer of Serous pericardium):** *Lasts Anatomy Regional and Applied (Elsevier), 2003/ 265; API Textbook of Medicine 9th/ 737*

***The visceral layer of serous pericardium is insensitive to pain.*** *The visceral layer of the serous pericardium is supplied by the sympathetic trunk and branches of the vagus nerves which are Pain Insensitive*
*Fibrous pericardium and Parietal layer of the Serous Pericardium are supplied by the phrenic nerve and are pain sensitive*

*Note :*
*The pain of pericarditis typically originates only from the pain sensitive parietal layer (lower two thirds) and is transmitted by the phrenic nerve. Pain from the heart(angina) originates in the muscles and vessels and is transmitted by sympathetic nerves*

**328. Answer is B (Phrenic nerve):** *Clinically Oriented Anatomy by Moore (Lippincott Williams & Wilkins) 7th/ 131;*

***The phrenic nerve (C3, 4, 5) provides sensory innervation to the fibrous and parietal layers of the pericardium.*** *When pain sensitive areas of pericardium are stimulated by disease, pericardial pain is perceived as pain in the neck and around the trapezius muscle via the phrenic nerve (The skin above the clavicle (C3, 4, 5 dermatomes))*

**Nerve Supply of The Pericardium**

- ***Phrenic nerves (C3-C5)*** (This is the primary source of sensory fibres)
  Pain sensations conveyed by these nerves are commonly referred to the skin (C3-C5 dermatomes) of the ipsilateral supraclavicular region (top of the shoulder of the same side).
- *Vagus nerve* (Their function is uncertain)
- *Sympathetic trunks* (Vasomotor)

*Note: The phrenic nerve does not innervate the heart but does give off somatosensory branches to the pericardium (pericardial branches) in the middle mediastinum on its way to the diaphragm*

*Note: The phrenic nerve only innervates the pericardium and does not innervate the heart*

**329. Answer is A (Cardiac tamponade):** *Harrison 14th/ 1336, Harrison 15th/ 1270, 1367; Harrison 17th/ 1396* Harrison 18th/p 1839, 1975

*Electrical alternans refers to a beat-to-beat alteration in one or more components of the ECG signal.*
***Total electrical alternans (P-QRS-T) with sinus tachycardia is a relatively specific sign for pericardial effusion, often with cardiac tamponade.*** *– Harrison 16th / 1319*

| *Feature* | Cardiac Tamponade | Constrictive Pericarditis | Restrictive Cardiomyopathy | RVMI |
|---|---|---|---|---|
| Electrical Alternans | *May be present* | Absent | Absent | Absent |

## Constrictive Pericarditis

**330. Answer is D (Constrictive pericarditis):** *Robbins 7th/601, 602; Robbins Patho Illustrated 6th/ 589*

***Constrictive pericarditis is not haemorrhagic***

**Causes of haemorrhagic pericarditis:** *Robbins 7th/601, 602*

*Bacterial infections: infective endocarditis*
*Tuberculosis*
*Bleeding diathesis*
*Following cardiac surgery*
***Ruptured MI***
***Ruptured aortic dissection***
***Traumatic perforation***

*The latter four conditions are mentioned as causes of haemorrhagic pericardial effusion or hemopericardium.*

**331. Answer is D (Rheumatic fever) :** *Harrison 16th / 1418, 1978; Harrison 17th/ 1493* Harrison 18th/p 1976

***Rheumatic fever has not been mentioned in association with constrictive pericarditis.***
***"Although Rheumatic pericarditis can cause a serous effusion, fibrin deposits and even pericardial calcification, it does not lead to constrictive pericarditis." - Harrison 16th/1978***

**Causes of constrictive pericarditis :** - *Harrison 16th / 1418*

- Trauma
- ***Cardiac operation of any type***
- Mediastinal irradiation
- ***Purulent infection (Staph. effusion)***
- ***Histoplasmosis / Tuberculosis***
- Neoplastic disease especially breast cancer, lung cancer and lymp
- Acute viral pericarditis
- Rheumatoid arthritis, SLE
- Chronic renal failure with uremia treated by chronic dialysis
- Idiopathic

*In the past **Tuberculosis** was the most common cause but the process not more often occurs after radiation therapy. **Cardiac surgery** or viral pericarditis. Histoplasmosis is another uncommon cause. - CMDT 2006/409*

**332. Answer is A (Commonest cause in India is 'Idiopathic'):** Harrison 18th/p 1975, 1976 *Harrisons 17th/ 1493 Kelly's Essentials of Medicine 2nd/119*

***The commonest cause of constrictive pericarditis in developing countries including India is tuberculosis***

**Commonest cause of constrictive pericarditis in India is Tuberculosis**

*Commonest cause of contrictive pericarditis in developing countries is tuberculosis.*

*Commonest cause of constrictive pericarditis in North America is 'Idiopathic' – Kelly's Essentials of Medicine 2nd /119*

*Commonest cause of constrictive pericarditis*

| Developed Nations | Developing Nations |
|---|---|
| • ***Post viral pericarditis or Idiopathic pericarditis*** | ***Tuberculosis*** |
| • *Previous cardiac surgery* | |
| • *Chest Radiation therapy* | |

**Kussmaul's sign is positive in constrictive pericarditis** (Harrisons 17th/1491)

| Feature | Tamponade | Constrictive pericarditis | Restrictive cardiomyopathy | RVMI |
|---|---|---|---|---|
| *Kussmaul's sign* | *Absent (Rare)* | ***Present*** | *Present* | *Present* |

**Ascitis in constrictive pericarditis is out of proportion to peripheral Edema** *(CMDT 2007/419)*

*'Ascitis often seems out of proportion to degree of peripheral edema (CMDT)*

**Right ventricular End Diastolic pressure is raised in constrictive Pericarditis**
*'In constrictive pericarditis ventricular end diastolic volume and stroke volume are reduced and the end diastolic pressures in both ventricles are elevated' - Harrison*

**333. Answer is D (Acute Pulmonary Edema):** Harrison 18th/p 1976 *Harrisons 17th/1493*

*Acute Pulmonary Edema is not a usual feature of constrictive pericarditis.*
*Constrictive Pericarditis represents a chronic process of fibrosis, scarring and calcification that continues for months or years. Acute left ventricular failure or Acute Pulmonary Edema is very uncommon in constrictive pericarditis.*

**Ascites is a common presenting feature of constrictive pericarditis**
*Ascites is common and is usually more prominent than dependent edema*
*Ascites often seems out of proportion to peripheral edema (CMDT)*

**Apex beat in constrictive Pericarditis may be Retractile**
*The Apical pulse is reduced and may retract during systolic (Broad bent's sign) – Harrisons 17th/1994*
*Inward motion of the apex beat called Apical Retraction suggests constrictive Pericarditis*

**Pericardial knock is a charachteristic feature of constrictive Pericarditis**
*Pericardial knock is produced as a result of abrupt cessation of ventricular filling as a result of fibrotic and thickened pericardium.*

| Feature | Tamponade | Constrictive pericarditis | Restrictive cardiomyopathy | RVMI |
|---|---|---|---|---|
| *Pericardial knock* | *Absent* | ***Often present*** | *Absent* | *Absent* |

**334. Answer is D (Constrictive pericarditis):** Harrison 18th/p 1976 *Harrisons 17th/1493; Current Diagnosis & Treatment in Cardiology 2nd/ 214, 215 CMDT 2007/419*

*Square Root sign is a characteristic (but not pathognomic) feature of constrictive pericarditis.*

**Square root sign : Dip and Plateau wave form**

- 'The square root sign' describes the diastolic pressure waveform observed during ventricular pressure tracings on cardiac catheterization
- The wave form is called 'square root sign' as it is charachterized by an early diastolic dip followed by a high diastolic plateau with an elevated end diastolic pressure resembling the 'square root sign'.
  (It results from early rapid diastolc filling with sudden cessation as the pericardium reaches its compliance limit)
- This sign is also called 'dip and plateau' sign
- The square root sign is charachtristic of constrictive pericarditis but it is not pathonognomic of constrictive pericarditis.
  The square root sign may also be found in restrictive cardiomyopathy

| **Square Root sign** |
|---|
| *Constrictive Pericarditis (More Prominent)* |
| *Restrictive cardiomyopathy (Less prominent)* |
| *Square root sign is more prominent in constrictive pericarditis than restrictive cardiomyopathy* |

**335. Answer is A and C (Diastolic Pressure are equalized; Thick pericardium is present):** Harrison 18th/p 1975 *Harrisons 17th/1491; Refer previous table*

*Diastolic pressure are equalized in constrictive pericarditis but not in Restrictive cardiomyopathy*
*Thickenned pericardium is seen in constrictive pericarditis but not in Restrictive cardiomyopathy*

*Right ventricular size is usually normal in both and pericardial effusion is usually absent in both, RV size and pericardial effusion, therefore can not distinguish between constrictive pericarditis and Restrictive cardiomyopathy*

| Feature | Constrictive Pericarditis | Restrictive Cardiomyopathy |
|---|---|---|
| • Thickenned pericardium | *Present* | *Absent* |
| • Pericardial Effusion | *Absent* | *Absent* |
| • RV size | *Usually Normal* | *Usually Normal* |
| • Equalization of diastolic pressure | *Usually present* | *Usually Absent* |

**336. Answer is C (RVMI) :** Harrison 18th/p 1975 *Harrisons 17th/1491*

*Rapid 'x' descent is rare in RVMI*

| Feature | Tamponade | Constrictive Pericaditis | Restrictive Cardiomyopathy | RVMI |
|---|---|---|---|---|
| Prominent x descent | Present | Usually present | Present | ***Rare*** |
| Prominent y descent | Absent | Usually present | Rare | Rare |

## Hypertension

### General

**337. Answer is A (Essential Hypertension):** *Harrison*

*Most common cause of Hypertension in adults is Essential Hypertension.*

*Essential (primary or idiopathic) hypertension is the most common cause of hypertension in adolescents and adults.*

**338. Answer is A (Gender):** *Harrison 18th/ Chapter 247.*

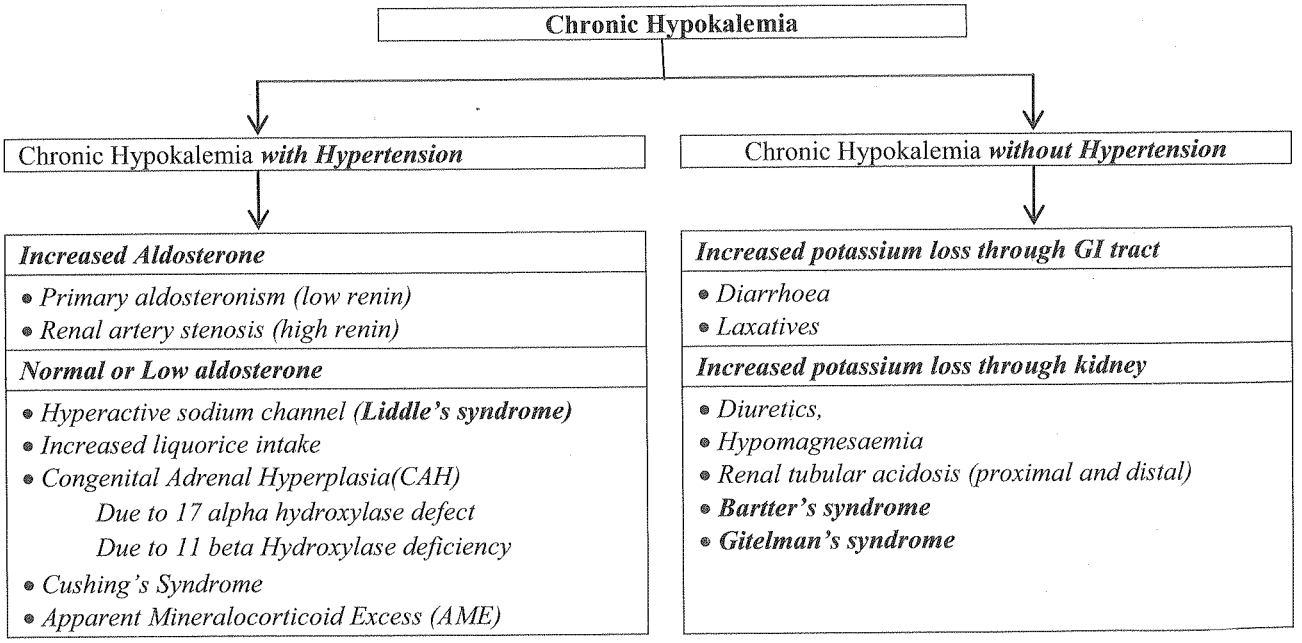
*Age, Gender, Race and Genetic influences are non-modifiable risk factors for hypertension.*

**339. Answer is A (Gender/Sex)**

***Gender/Sex is a non-modifiable risk factor for Hypertension.***

**340. Answer is B (Liddle's Syndrome):** Refer Review Notes on Liddle's Syndrome

*Liddle's Syndrome is typically associated with Hypokalemia and Hypertension. Bartter's Syndrome and Gitelman's Syndrome are also associated with hypokalemia but without hypertension.*

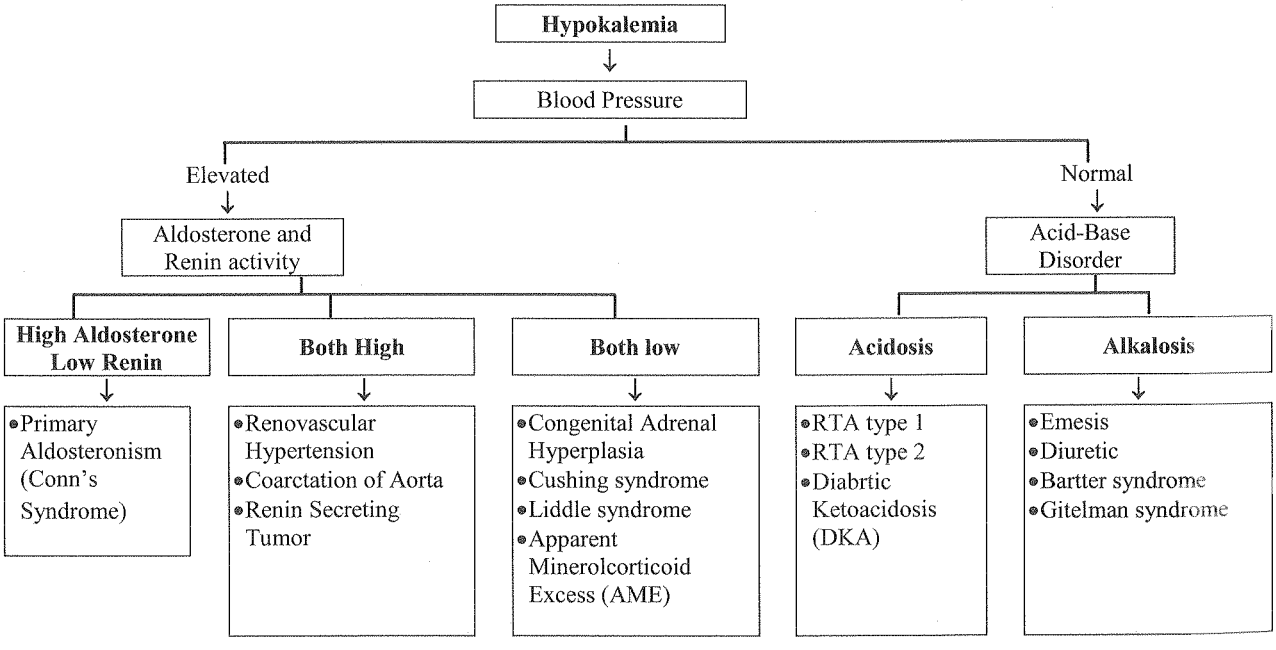


| *Liddle's Syndrome : Review* |
|---|
| ***Pathophysiology:*** |
| • *Autosomal dominant disorder.*<br>• *Genetic defect in the collecting tubule sodium channel, resulting in increased sodium reabsorption and lack of inhibition by higher levels of intracellular sodium* |
| ***Age of Presentation*** |
| • *Often diagnosed at young age, but can present in adulthood due to phenotypic variation.* |
| ***Clinical presentation*** |
| • *Classic triad of hypertension, metabolic alkalosis, and hypokalemia.*<br>• *Consider if family history of hypertension and/or hypokalemia, at young age* |
| ***Lab data*** |
| • *Metabolic alkalosis, hypokalemia (although some are low normal), low urinary aldosterone secretion* |
| ***Treatment:*** |
| • *Lifelong. Potassium-sparing diuretic which closes the sodium channel (Amiloride or Triamterene). Spironolactone does not work because aldosterone is not causing the sodium channel to be open.* |

**341. Answer is A (Renal Artery Stenosis):** *Multiple references*

*The association of High aldosterone and High Renin levels in a hypertensive patient with hypokalemia suggests a diagnosis of Secondary Hyperaldosteronism from Renal Artery Stenosis.*

| *Disease* | *Aldosterone* | *Cortisol* | *Renin* |
|---|---|---|---|
| *Primary Aldosteronism (Conn syndrome)* | *High* | *Normal* | *Low* |
| *Secondary Aldosteronism (e.g. Renal Artery Stenosis)* | *High* | *Normal* | *High* |
| *Adrenal insufficiency (Addison disease)* | *Low* | *Low* | *High* |
| *Cushing syndrome* | *Low (May be normal)* | *High* | *Low* |




**342. Answer is C (Diet modification, exercise & drugs):** *Harrison 18th /2054*

***Management of uncomplicated essential hypertension includes health promoting lifestyle modifications (includes dietry modification & exercise) and pharmacological therapy (drugs).***

**Management of Uncomplicated Essential Hypertension**

**Lifestyle modification**

| | |
|---|---|
| Weight reduction | Attain and maintain BMI <25 kg/m$^2$ |
| Dietary salt reduction | <6 g NaCl/d |
| Adapt DASH-type dietary plan | Diet rich in fruits, vegetables, and low-fat dairy products with reduced content of saturated and total fat |
| Moderation of alcohol consumption | For those who drink alcohol, consume 2 drinks/day in men and 1 drink/day in women |
| Physical activity | Regular aerobic activity, e.g., brisk walking for 30 min/d |

**Pharmacological Therapy**

- In uncomplicated essential hypertension the treatment is started with a low-dose thiazide (hydrochlorothiazide 12.5-25 mg per day), an ACE inhibitor or a beta-blocker.
- Calcium-channel blocker can be used as the first-line treatment if the systolic pressure is high.
- Angiotensin-II receptor antagonists should be considered when the adverse effects of ACE inhibitors or other drugs have proven problematic.
- If no response is achieved, or adverse effects emerge, a product of another drug group should be prescribed.
- Combination therapy is started if desired blood pressure reduction is not achieved with monotherapy.
- The reasons behind poor response must be established.

**343. Answer is A (ACE inhibitors and Beta blockers):** *API 6th/537: Harrisons 16th/1479*

*Combination therapy involving ACE inhibitors and Beta blocker is not recommended.*

**Drug combination in Hypertension**

| Useful Combinations | Undesirable Combinations |
|---|---|
| ACE inhibitor and calcium blocker (A+C) | Low dose diuretic and calcium blocker |
| ACE inhibitor (or AII receptor antagonist) and diuretic (A+D) | Beta-blocker and verapamil/diltiazem |
| Beta-blocker and Calcium blocker (amlodipine) (B+C) | Beta-blocker and ACE inhibitor |
| Diuretic and beta-blocker (B+D) | Two drugs from the same class |

**Combination Therapy** *(Harrisons 16th/1479)*

For Medium to high risk patients strongly consider low dose combination therapy as initial therapy

| Diuretic with Beta blocker or ACE inhibitor (or Angiotensin Antagonist) | Calcium channel blocker with ACE inhibitor or Beta blocker |
|---|---|

**Rational Combination therapies : Step-wise approach (API textbooks)**

| | *Younger* | *Older* |
|---|---|---|
| Step 1 | A (or B*) | C or D |
| Step 2 | A (or B*) + C or D | |
| Step 3 | A (or B*) + C + D | |
| Step 4 Resistant Hypertension | Add: either a-blocker or spironolactone or other diuretic | |

A : ACE inhibitor or angiotensin receptor blocker B: β-blocker
C : Calcium channel blocker D : Diuretic (thiazide)

**344. Answer is A (Beta Blockers):** *Evidence Based Medicine Guidelines (John Wiley & Sons) 2005/4.26; 'Hypertension: A companion to Braunwald's Heart Disease (Elsevier) 2007/335*

***Beta-blockers are the first line drugs of choice for treatment of hypertension in patients with coronary artery disease & stable angina***

*'Beta blockers are the first line choice when treating hypertension in a patient with coronary artery disease' – Evidence Based Medicine Guidelines (John Wiley & Sons)*

*'Beta blockers reduce angina symptoms, improve mortality and lower BP, and they should be the drugs of first choice in hypertensive patients with CAD and stable angina' – 'Hypertension: A companion to Braunwald's Heart Disease'*

**345. Answer is A (Beta-Blockers):** *Braunwald 9th/ Chapter 57*

***Beta Blockers are recommended as First Line Agents of choice for treatment of hypertension in hypertensive patients with Stable Ischemic Heart Disease.***

**346. Answer is A (Lisinopril):** *Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine 10th/ 977,978; (JNC-8 Guidelines: http://www.measureuppressuredown.com/HCProf/Find/BPs/JNC8/specialCommunication.pdf)*

***Lisinopril (ACE Inhibitor) is recommended as the first line antihypertensive therapy for patients with diabetes***
*All patients with diabetes and hypertension should be treated with a regimen that includes ACE Inhibitor or ARB. If one class is not tolerated it should be substituted with another class. First add-on therapy may include a Thiazide diuretic or Calcium channel blocker (ACE-I + CCB >= ACE-I + Thiazide). Beta blockers are also beneficial in the treatment of hypertension with diabetes. However since these agents can cause hyperglycemia, they should be reserved as the third or fourth add-on agents for controlling blood pressure.*

**Which Antihypertensive Drugs for which patients?**

- There is general consensus that at the end of the day, the vast majority of hypertensive patients—regardless of age, race/ethnicity, and absence or presence of target organ damage or comorbid conditions—will requires triple combination drugs therapy with a CCB, an ACEI or ARB, and a diuretic. The only issue is which drug or drugs to prescribe first.
- ***There is overwhelining consensus that an ACEI or ARB is first-line antihypertensive therapy for patients with diabetes.***
- ***There is overwhelming consensus that an ACEI or ARB is first-line antihypertensive therapy for patients with CKD.***

**Note:**
*Most guidelines prefer both a thiazide and a CCB over an ACEI or ARB* ***to initiate therapy in black patients.***

**Comparison of 2003 JNC 7 Guidelines with New Recommendations common to the Guidelines by the 2014 JNC-8 Committee, 2013 ESH/ESC, 2011 UK-NICE, and 2011 ACCF,AHA**

| | 2003 JNC 7 REPORT | 2011-2014 GUIDELINES |
|---|---|---|
| **Blood pressure threshold for initiation of drugs therapy** | *≥140/90 mm Hg for most patients ≥130/80 mm Hg for patients with diabetes or CKD* | ≥150/90 mm Hg for elderly patients ≥140/90 mm Hg for nonelderly patients and patients with Diabetes or CKD |
| **First-line therapy** | *Thiazide diuretic for most patients* | Three first-line drug classes; CCB, ACEI or ARB, Thiazide |
| **Preferred thiazide** | *Hydrochlorthiazide (HCTZ)* | Chlorithalidone |
| **Combination drug therapy** | *Mainly for stages 2 hypertension ACE-I + Thiazide* | A good option for stage I hypertension ***ACE-I + CCB ≥ ACE-I + thiazide*** |

**347. Answer is C (Enalaprilat):** *Harrisons 16th/1478,1479*

*The presence of proteinuria in this diabetic patient suggest a diagnosis of diabetic nephropathy.*

***The drugs of choice for management of hypertension in patients with diabetes are ACE inhibitors***
***Enalapril is an ACE inhibitor and the drug of choice for management of hypertension in patients with diabetic nephropathy.***

*ACE inhibitors or Angiotensin blockers should be the first line therapy in hypertensive individuals with type 2 Diabetes. They have no known adverse effect on glucose or lipid metabolism and minimize the development of diabetic nephropathy by reducing renal vascular resistance and renal perfusion pressure- Harrison*

| Indication | | Treatment of choice |
|---|---|---|
| *Hypertensive patient with protenuria*$^{Q}$ | - | *ACE inhibitors or Angiolensin Blocker* |
| *Hypertensive patient with Diabetes*$^{Q}$ | - | *ACE inhibitors or Angiotensin Blocker* |
| *Hypertensive patient with diabetic Nephropathy*$^{Q}$ | - | *ACE inhibitor or Angiotensin Blocker* |

*ACE inhibitors have become the drug of choice for chronic renal disease whether diabetic or non diabetic in origin.*
*– Braunwald 8th/1063.*

**348. Answer is C (Enalapril):** *Refer previous question*

***ACE inhibitors (Enalapril) are the agents of choice for treatment of hypertension in diabetic patients with proteinuria.***

| Indication | | Treatment of choice |
|---|---|---|
| *Hypertensive patient with protenuria*$^{Q}$ | - | *ACE inhibitors or Angiolensin Blocker* |
| *Hypertensive patient with Diabetes*$^{Q}$ | - | *ACE inhibitors or Angiotensin Blocker* |
| *Hypertensive patient with diabetic Nephropathy*$^{Q}$ | - | *ACE inhibitor or Angiotensin Blocker* |

**349. Answer is C (Oral Enalapril):** *API 8th/532, 537*

***Oral Enalapril (ACE inhibitors) are effective in lowering blood pressure and are well tolerated.***

***Oral Enalapril is the agent of choice amongst the options provided.***

*Hypertensive emergencies/urgency are defined when Diastolic BP> 120; Systolic BP>220.*

*The patient in question has a blood pressure of 190/120 mmHg.*

*This is not a case of hypertensive emergency/urgency and hence rapid lowering of blood pressure is not warranted. Blood pressure in such cases may be adequately normalized by an ACE inhibitor therapy which is the treatment of choice amongst the options provided*

***IV Nitroglycerine, Oral Nitroglycerine, IV Enalapril and Sublingual Nifedipine*** *cause rapid lowering of blood pressure which is not indicated in this patient.*

**350. Answer is B,C,E (Gordon's syndrome; Pregnancy Exacerbated HTN; Glucocorticoid-remediable hyperaldosteronism):** *Harrison 17th/1557*

***Rare monogenic forms of hypertension that are inherited as Autosoma l Dominant traits include Gordon's syndrome, Pregnancy Exacerbated HTN and Glucocorticoid-remediable hyperaldosteronism***
*17- α Hydroxylase deficiency ay also present as a rare form of monogenic hypertension but this is inherited as an Autosomal Recessive trait*

**Monogenic form of hypertension**
**Mandelian Forms of Hypertension (Rare)**

| Autosomal dominant | Autosomal recessive |
|---|---|
| • *Glucocorticoid-remediable hyperaldosteronism*<br>• *Liddle's syndrome*<br>• *Pseudohypoaldosteronism type II (Gordon's syndrome)*<br>• *Hypertension exacerbated in pregnancy (apparent mineralocorticoid excess syndrome)*<br>• *Polycystic kidney disease*<br>• *Pheochromocytoma* | • *17α-hydroxylase deficiency*<br>• *11 β -hydroxylase deficiency*<br>• *11 β -hydroxysteroid dehydrogenase deficiency* |

## Hypertensive Crisis

**351. Answer is D (All of the above):** *Braunwald 8th/1045*

***Acute Aortic Dissection, Hypertensive Encephalopathy and Intracerbral haemorrhage are all hypertensive emergenices that require rapid reduction of blood pressure***

Indications for rapid reduction of BP

- Rapid reduction of blood pressure is indicated in hypertensive emergencies and hypertensive urgencies(Braunwald)
- Hypertensive emergencies require very rapid reduction or immediate reduction in blood pressure preferably within minutes (within 1 hour) Hypertensive urgencies also require rapid reduction but, reduction required is not immediate and can be achieved more slowly over hours (or over days)

Clinical Circumstances requiring rapid reduction of BP (Braunwald 8th/1045)
(Hypertensive Emergencies and Hypertensive Urgencies)

- Accelerated-malignant hypertension with papilledema
- Cerebrovascular
  - Hypertensive encephalopathy
  - Atherothrombotic brain infarction with severe hypertension
  - Intracerebral hemorrhage
  - Subarachnoid hemorrhage
- Cardiac
  - Acute aortic dissection
  - Acute left ventricular failure
  - Acute or impending myocardial infarction
  - After coronary bypass surgery
- Renal
  - Acute glomerulonephritis
  - Renal cries from collagen-vascular diseases
  - Severe hypertension after kidney transplantation
- Excessive circulating catecholamines
  - Pheochromocytoma crisis
  - Food or drug interactions with monoaime oxidase inhibitors
  - Sympathomimetic drug use (cocaine)
  - Rebound hypertension after sudden cessation of antihypertensive drugs
- Eclampsia
- Surgical
  - Severe hypertension in patients requiring immediate surgery
  - Postoperative hypertension
  - Postoperative bleeding from vascular suture lines
- Severe body burns
- Severe epistaxis
- Thrombotic thrombocytopenic purpura

**352. Answer is A (Hypertensive urgency is characterized by marked elevation of blood pressure and rapidly evolving end organ damage):** *Braunwald 8th/1045; Harrisons 17th/1561,1562; Hurst 12th/1625*

***Rapidly evolving end organ damage is a feature of hypertensive emergency and not hypertensive urgency.***

*Hypertensive urgency is defined by a markedly elevated blood pressure usually in the same range as seen in hypertensive emergencies but <u>without</u> the rapid progression of target organ damage.-Hurst 12th/1625*

Hypertensive Crisis

| Hypertensive Emergencies | Hypertensive urgencies |
|---|---|
| • Marked elevation of Blood pressure with rapidly evolving end organ damage.<br>• No fixed Blood pressure cut off values are defined but, in general the blood pressure values are as follows. Diastolic BP> 120; Systolic BP>220<br>• Rapid /Immediate reduction of blood pressure is indicated in these patients<br>• Blood pressure should be controlled within hours (Preferably within 1 hours)<br>• Intensive monitoring in a critical care setting is mandatory | • Marked elevation of blood pressure without rapidly evolving end organ damage<br>• No fixed blood pressure cut off values are defined but in general the blood pressure values may approach the same range as seen in hypertensive emergencies<br>• Lowering of blood pressure is essential but immediate very rapid reduction is often not required<br>• Blood pressure should be controlled over a period of hours or days (Preferably within 24 hours)<br>• Intensive monitoring in a critical care setting is not always required<br>*If the patient is asymptomatic or clinically stable the patient can be managed as an outpatient with dose follow up within days without an intensive monitoring setting usually with oval medications – Hurst 12th/1625* |

**353. Answer is C (Indapamide):** *Braunwald 8th/1066; API 8th/538; KDT 6th/115; Hurst 12th/1626*

***Indapamide is a mild diuretic that may be used for treatment of mild to moderate hypertension. It is not effective in the treatment of hypertensive urgencies or emergencies.***

Commonly used Drugs in the Management of Hypertensive Crisis

| Common Intravenous Agents (Used for Hypertensive Emergencies) | Common Oral Agents (Used for Hypertensive Urgencies) |
|---|---|
| **Diuretics**<br>*Furosemide*<br>**Vosodilators**<br>*Sodium Nitroprusside*<br>*Nitroglycerine*<br>*Fenoldapam*<br>*Nicardipine*<br>*Hydralazine*<br>*Enolaprilant*<br>**Adrenergic Inhibitors**<br>*Phentolamine*<br>*Esmolol*<br>*Metaprolol*<br>*Labetolol*<br>*Urapidil* | *Nifedipine (Not Recommended now)*<br>*Nicardipine*<br>*Israpidine*<br>*Clonidine*<br>*Coptopril*<br>*Labetolol*<br>*Hydralazine*<br>*Nitroglycerine* |

**** Nifedipine should be used with great caution 'if at all' according to the US F.D.A.'***

**354. Answer is B (Labetalol):** *Harrison 17th /1561, 1562; Hurst 12th/1625*

***Symptomatic Hypertension with diastolic pressure of 120 suggest a diagnosis of Hypertensive Emergency. Labetalol (intravenous) is the drug of choice for management of Hypertensive Emergencies (amongst the options provided).***

**355. Answer is D (Indapamide):** *KDT 6th/115,342 : API 8th/538; Hurst 12th/1626; Braunwald 8th/1066*

***Indapamide is a mild diuretic that may be used for treatment of mild to moderate hypertension It is not effective for the treatment of hypertensive urgencies or emergencies where rapid reduction of blood pressure is required. Indapamide is the single best answer of exclusion.***

**Trimethophan (KDT 6th/115)**

Trimethophan is an ultrashort acting ganglion blocker

*IT has been occasionally used in treatment of hypertensive emergencies due to Aortic dissecton (KDT)*

**Nifedipine (KDT 6th/554)**

*Nifedipine may be employed for rapid reduction of BP in hypertensive urgencies although its use is not recommended*
*Nifedipine was once one of the most popular drugs used hypertensive urgencies*

**Hydralazine**

*Hydralazine is an effective agent for the management of hypertensive urgencies and emergencies.*

**356. Answer is D (Clonidine):** *Braunwald 8th/1066; API 8th/538; Hurst 12th/1626; 'Koda-kimble and young's manual of Therapeutics: Clinical use of Drugs' (Lippincott William) 2012/525*

***Clonidine is a central Alfa-agonist that is recommended for the management of severe hypertension, that is not accompanied by evidence of end organ damage. However clonidine is not recommended for true hypertensive emergencies (crisis) where the goal is to reduce the blood pressure within minutes (preferably in less than one hour)***

*Fenoldapam, Nitroglycerine and Nitroprusside may all be used intravenously for rapid reduction of Blood Pressure in patients with true Hypertensive emergencies.*

**Commonly used Drugs in the Management of Hypertensive Crisis**

| Common Intravenous Agents (Used for Hypertensive Emergencies) | Common Oral Agents (Used for Hypertensive Urgencies) |
|---|---|
| **Diuretics**<br>*Furosemide*<br><br>**Vosodilators**<br>*Sodium Nitroprusside*<br>*Nitroglycerine*<br>*Fenoldapam*<br>*Nicardipine*<br>*Hydralazine*<br>*Enolaprilant*<br><br>**Adrenergic Inhibitors**<br>*Phentolamine*<br>*Esmolol*<br>*Metaprolol*<br>*Labetolol*<br>*Urapidil* | *Nifedipine (Not Recommended now)*<br>*Nicardipine*<br>*Israpidine*<br>*Clonidine*<br>*Coptopril*<br>*Labetolol*<br>*Hydralazine*<br>*Nitroglycerine* |

**** Nifedipine should be used with great caution 'if at all' according to the US F.D.A.'***

**357. Answer is D (Nifedipine):** *KDT 6th/554; Harrisons 16th/1475; Cardiac drug therapy by Gabriel Khan 7th/128,129; Kidney and hypertension by Bakris (2004)/146*

*Nifedipine is used as an oral/sublingual agent. It is not available for intravenous administration.*

**Nifedipine in Hypertensive Urgencies**

- Nifedipine is a short acting Dihydropyridene calcium channel blocker
- Nifedipine may be employed for rapid reduction of blood pressure in hypertensive urgencies but it is not recommended for such use because it has been reported to increase the incidence of acute coronary events.
- According to the US Food and Drug administration Nifedipine should be used with great caution 'if at all'
- ***Nifedipine is available for oral administration only and cannot be administered intravenously***

***Urapidil*** *(Cardiac drug therapy by Gabriel khan 7th/128,129)*

- Urapidil is a selective alpha 1 adrenoceptor antagonist effective in the treatment of hypertensive emergencies.
- It may be administerd intravenously and is also available for oral administration

**Fenoldopam** *(Hurst 12th/1626)*

- Fenoldopam is a selective dopamine -1 Receptor Agonist effective in the treatment of hypertensive emergencies
- It is available for intravenous administration.

**Enalaprilat**

- Enalaprilat is an ACE inhibitor effective in the treatment of hypertensive emergencies
  *(Enalaprilat is the active of Enalapril that is available for intravenous administration. Enalapril can only be administered orally).*

**358. Answer is A, C and E (Nifedipine, Phenoxybenzomine, Labetalol) :** *Refer text below*

*A blood pressure recording of 200/120 with symptoms of headache and sweating suggests a diagnosis of Hypertensive crisis (urgency / Emergency).* ***Nifedipine, Methyl Dopa and Phenoxybenzamine arenot preferred in the treatment of Hypertensive crisis***

**Nifidipine, Methyl Dopa and phenoxybenzamine are not preferred for treatment of Hypertensive crisis**

- **Nifedipine** was once one of the most popular drugs used in hypertensive urgencies, but its use is no longer recommended since it has been reported to increase the risk of acute coronary events.
  *'Short acting nifedipine has no role in the treatment of hypertension' – Harrison*
  *'Nifedipine should be used with great caution 'if at all' according to the USFDA'*

- **Methyl Dopa** has a relatively slow onset of action. It is not a preferred agent for treatment of hypertensive crisis owing to its adverse effect profile and because of its relatively slow action . It is now usually reserved for the treatment of hypertension in pregnancy

| Preferred Agents for Treatment of Hypertensive Crisis of Pregnancy |
|---|
| *Hydralizene, Labetalol, Nicardipine* |

- **Phenoxybenzomine is a long acting alpha adrenergic blocker that can produce a 'Chemical sympathethectomy'**

  Phenoxybenzamine is primarily used to control episodes of hypertension in patients with pheochromocytoma and in preoperative management of hypertension in patients with pheochromocytoma, who are being prepared for surgery. *It has a relatively slow onset of action is and is not preferred for the management of hypertensive crisis even in patients with pheochromocytoma*

| Preferred Agents for Treatment of Hypertensive crisis in pheochromocytoma (Adrenergic / catecholamine crisis) |
|---|
| *Phentolamine, Nitroprusside, Labetalol* |

**Sodium Nitropnesside and Labetalol are preferred agents for treatment of Hypertensive Crisis**

| **Preferred parenteral drugs for selected hypertensive emergencies** | |
|---|---|
| *Hypertensive encephalopathy* | ***Nitroprusside***, nicardipine, ***labetalol*** |
| *Malignant hypertension (when IV therapy is indicated)* | ***Labetalol***, nicardipine, ***nitroprusside***, enalaprilat |
| *Stroke* | Nicardipine, **labetalol**, *nitroprusside* |
| *Myocardial infarction/unstable angina* | Nitroglycerin, nicardipine, ***labetalol***, esmolol |
| *Acute left ventricular failure* | Nitroglycerin, enalaprilat, loop diuretics |
| *Aortic dissection* | ***Nitroprusside***, esmolol, labetalol |
| *Adrenergic crisis* | Phentolamine, ***nitroprusside*** |
| *Postoperative hypertension* | Nitroglycerin, ***nitroprusside, labetalol***, nicardipine |
| *Preeclampsia/eclampsia of pregnancy* | Hydralazine, ***labetalol***, nicardipine |

**359. Answer is D (Metabolic Alkalosis):** *Harrison 17th/293; Harrison 16th/268; Therapy of Renal Disease and Related disorders 2nd/169*

***Accelerated Hypertension is associated with metabolic alkalosis.***

*Accelerated Hypertension is a state in which there is renal underperfusion, high renin and increased aldosterone. This may result in hypokalemia and metabolic alkalosis.*

## Renovascular Hypertension



**360. Answer is B (CT Angiography):** *Harrison 16th/1470; Braunwald 8th/1040; The Cleveland Clinic Cardiology Board Review (Lippincott Williams) 1st/514*

***Spiral CT scan with intravenous contrast (CT angiography) is the most sensitive and specific test amongst the options provided.***

Note:
*Magnetic Resonance Angiography (MRA) has now emerged as the diagnostic test of choice at several centres with a sensitivity and specificity similar or even better than CT Angiography.*
*However as MRA has not been provided amongst the options, CT Angiography remains the single best answer of choice.*
*MRA is also more likely to be used more widely* ***(preferred)*** *because it reduces the possibility of contrast induced nephrotoxicity and avoids exposure to ionizing radiations.*

**Renovascular Hypertension**

| Screening Test of Choice | Gold Standard Diagnostic Test |
|---|---|
| Magnetic Resonance Angiography (MRA)<br>Spiral CT or Angiography (CTA) | Renal Angiography / Arteriography (conventional) |

***MRA is now emerging as the screening test of choice***

**361. Answer is A (Magnetic Resonance Angiography (MRA):** *'The Clevland Clinic Board Review' (Lippincott Williams) 1st/514; Harrison 16th/1470; Cardiovascular Therapeutic 3rd*

***Magnetic Resonance Angiography (MRA) has now emerged as the most sensitive and specific screening test for Renovascular hypertension.***
Note:
*Harrison 16th edition (old) mentions Spiral CT scan as the most sensitive and specific screening test for Renovascular Hypertension, however most recent textbooks now prefer MRA as the screening test of choice with similar or even better sensitivity and specificity than spiral CT Angiography.*

Renovascular Hypertension

**Screening Test**

| Test | Sensitivity (%) | Specificity (%) |
|---|---|---|
| Magnetic resonance angiography (MRA) | 100 | 96 |
| Spiral computerized tomography | 98 | 94 |
| Captopril renogram | 70-93 | 95 |
| Duplex Doppler ultrasonography | 69-96 | 86-90 |
| IVP | ~75 | ~85 |

**Gold Standard / Diagnostic Test**

| Test | Sensitivity | Specificity |
|---|---|---|
| Conventional Renal Angiography | >99% | >99% |

**362. Answer is C (Condition is nearly always bilateral):** Harrison 18th/p 2375, 2376 *Harrisons 17th/- 1811-1812*

*Presence of hypertension (BP = 160 / 110) and bruit in bilateral flanks suggest a diagnosis of Bilateral Renal Artery Stenosis in this patient.* ***Renal Artery Stenosis is bilateral in 50% of cases and is not nearly always bilateral***

**ACE inhibitors (eg Enalapril) may deteriorate renal function in patients with Bilateral Renal Artery Stenosis**
*ACE inhibitors (eg Enalapril)* are the agents of choice for treatment of hypertension in patients with unilateral renal artery stenosis, but *are* ***contraindicated in patients with bilateral disease***. The presence of bruit in both flanks suggest *bilateral disease in this patient and hence enalapril should not be used*

**Contrast Enhanced Arteriography (Angiography) is the most definitive diagnostic procedure for the diagnosis of Renal Artery stenosis** while Magnetic Resonance Angiography (MRA) is the most sensitive and specific non invasive test (screening test) for its diagnosis.

**Fibromuscular dysplasia is the most common cause of Renal Artery stenosis in young women** while Atherosclerotic disease is the most common cause in middle aged/ elderly patients. *The patient in question is a young female (20 years) and hence the most likely cause of Renal Artery stenosis in this patient is fibromuscular dysplasia*

**Surgical Intervention may be required in patients with Bilateral Renal Artery Stenosis**
*Surgical intervention* in the form of angioplasty and stent placement is indicated when medical therapy has failed to control BP or resulted in > 30% increase in serum creatinine.

Renal Artery Stenosis: Review

- Renal Artery stenosis is an important cause of Renovascular Hypertension
- ***Bilateral involvement is seen in half of the affected cases (50%)***

Etiology

- Atherosclerotic disease : This is the most common cause in middle aged /elderly patients
- Fibromuscular Dysplasia : ***This is the most important cause in young females***

Presentation

- Hypertension
  - Abrupt onset of hypertension
  - Acceleration of previously well controlled hypertension
  - Refractory Hypertension
- Features of increased sympathetic neural activity (which is associated with Renovascular disease)
  - Flushing
  - Loss of nocturnal BP decrease
  - Putonomic instability
  - Rapid BP swings
- Progressive Renal failure / Azotemia

Diagnosis

| Magnetic Resonance Angiography (MRA) | Contrast Enhanced Arteriography |
|---|---|
| MRA is the most sensitive (>90%) and specific (95%) non invasive test for the diagnosis of RAS | Contrast enhanced angiography is the most definitive (but invasive) diagnostic procedure for diagnosis of RAS |

Management

**Medical Therapy with ACE Inhibitors or Angiotensin Receptor Blockers**

| Indications | Contra indications |
|---|---|
| **Unilateral Renal artery Stenosis**<br>- With hypertension & normal renal function (more effective than other antihypertensives)<br>- With hypertension & abnormal renal function (beneficial effect on survival without affecting renal function)<br>- With hypertension, diabetes, proteinuria and normal or abnormal renal function (effective antihypertensives) | **Bilateral Renal Artery stenosis**<br>ACE inhibitors or Angiotensin receptor blockers are contraindicated in patients with Bilateral renal artery stenosis or stenosis in a solitary kidney as their use in such patients leads to worsening of renal failure<br>(These patients are especially sensitive to decline in intraglomerular pressure) |

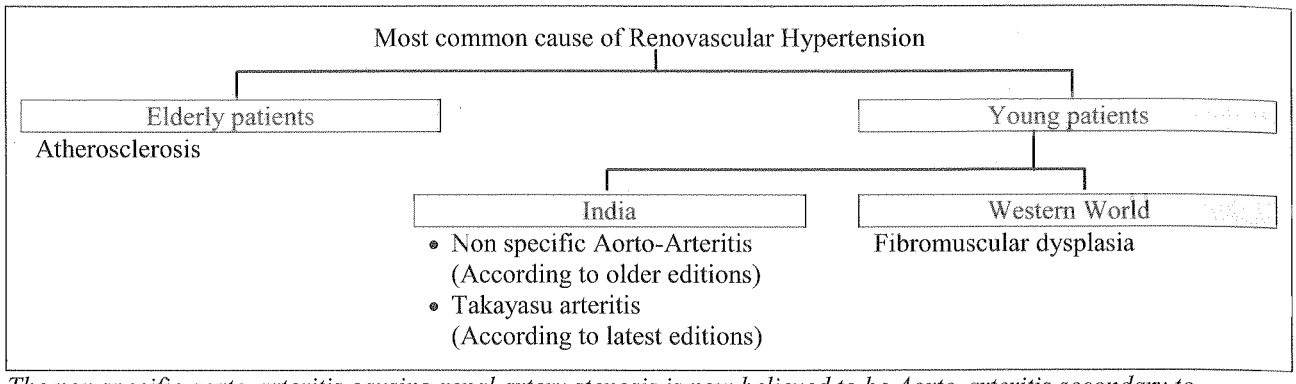
**Note**
***Acute Renal Failure / Worsening of Renal Failure with Angiotension Receptor Inhibitors is a diagnostic clue to the diagnosis of renal artery stenosis (indicates bilateral disease)***

**Surgical Therapy with Angioplasty + Stent placement**

*Should be considered only after optimal medical therapy has failed to achieve goal BP or resulted in a > 30% increase in serum creatinine*

**363. Answer is B (Non specific aorto-arteritis):** *Disease of kidney and urinary tract 8th/1279; Tropical Neurology 1st (2003)/440; Surgical Neuroangigraphy 2nd/115*

*The most common cause of renal artery stenosis in young adults in India is Non specific aorto-arteritis.*




*The non specific aorto-arteritis causing renal artery stenosis is now believed to be Aorto-arteritis secondary to Takayasu arteritis*

**Aorto-arteritis/Takayasu arteritis is the most common cause of renovascular hypertension in India**

*Non specific Aorto-arteritis is the most common cause of renovascular hypertension in India and China – Tropical Neurology 1st (2003)/440*

*Takayasu arteritis (Aorto-arteritis) is the most common cause of renovascular hypertension in India and China.' – Diseases of kidney and Urinary Tract 8th/1279*

*In India, China, Korea, Japan and other South East Asian countries, Takayasu arteritis is the most common cause of renovaascular hypertension.' – Surgical Neuroangiography 2nd/115*

Note:
*The non specific aorto-arteritis causing renal artery stenosis is now believed to be Aorto-arteritis secondary to Takayasu arteritis*

**364. Answer is D (Polyarteritis nodosa):** *Harrison 16th/1707,2007,2009; CMDT'06,460, API 8th.541; References alongside explanation*

***Amongst the options provided renal artery stenosis is least likely to be seen in association with Polyarteritis nodosa.***

- **Atherosclerosis and Fibromuscular disease**
  - Renal artery stenosis is produced predominantly by atherosclerotic occlusive disease (80% to 90% of patients) or fibromuscular dysplasia (10-15% of patients).- *CMDT'06 p 460*
  - The common cause of renal artery stenosis ***in the middle aged and elderly*** is an atheromatous plaque at origin of renal artery. *Harrison*
  - ***In younger women*** stenosis is due to intrinsic structural abnormalities of the arterial wall caused by a heterogenous group of lesions called 'fibromuscular dysplasia'. - *Harrison 16th/1707*
- **PAN or Takayasu arteritis ?**

  *Harrison, CMDT* do not mention PAN or Takayasu arteritis as a cause for renal artery stenosis.
  However, Takayasu arteritis is certainly a more common cause of renal artery stenosis than PAN.
  Takayasu arteritis (Aorto-arteritis) *is beleiveds to be the most common of renovascular hypertension in India and China. – Diseases of Kidney and Urinary Tract 8th/1279*

  **A number of research publications, however show Takayasu arteritis as a cause for renal artery stenosis.**

| Takayasu Arteritis | PAN |
|---|---|
| *Takayasu arteritis (Aorto-arteritis) is the most common cause of renovascular hypertension in India and China.' – Diseases of kidney and Urinary Tract 8th/1279* | Renal artery stenosis in a Case of PAN has only been described as an unusual association and published as a rare case report (single case)<br>***Reference :*** "PAN with renal Artery Stenosis": Indian Pediatrics Volume 41-Jan.17, 2004. |

PAN
Although renal involvement is seen in upto 60% of patients with PAN its pathology does not involve renal artery stenosis.

The pathology involves arteritis without glomerulonephritis and is characterised by aneurysms of small and medium sized arteries. **Stenosis of main renal artery is an unusual association'.**

*-Research paper, www. Indian paediatrics. net/Jan 2004/86.pdf*

**Causes of Renal artery stenosis :** *API 8th/541; Renal Artery Stenosis : Diagnosis and Management - IHJ : May-June 2002, Vol. 54/No. 3*

1. Atherosclerosis
2. Fibromuscular dysplasia
3. Non specific Aorto arteritis
4. Takayasu arteritis and giant cell arteritis (Takayasu > Giant cell)
5. Antiphospholipid syndrome
6. Transplant renal artery stenosis
7. Renal artery embolism
8. Dissecting aneurysm of aorta
9. Radiation arteritis

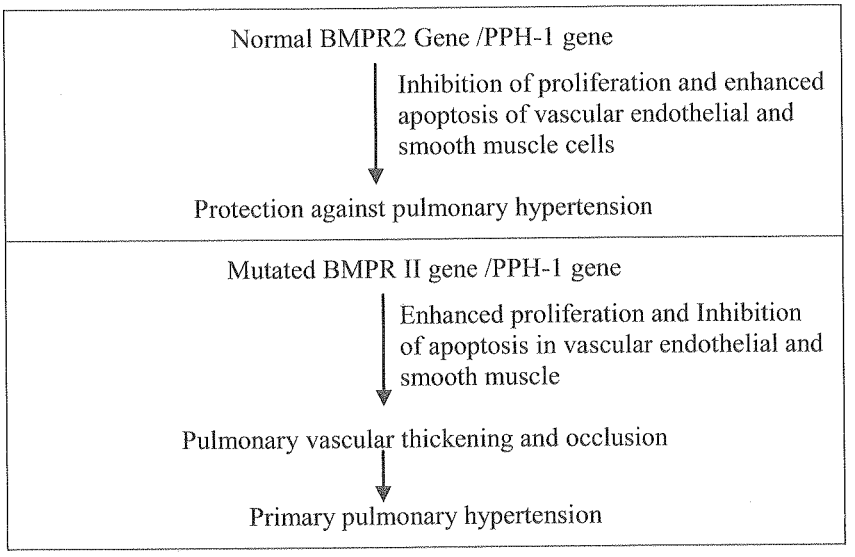
## Pulmonary Hypertension

**365. Answer is A (Bone morphogenic Receptor Protein II):** Harrison 18th/p 2077 *Harrisons 16th/1405; Harrisons 17th/1577; Robbins 7th /743,744*

***Gene coding the type II bone morhphogenetic protein receptor II (BMPR II) is associated with familial cases of primary pulmonary hypertension and designated as the PPH I gene.***

Bone morphogenic protein receptor II (BMPRII) and pulmonary Hypertension

- BMPRII is a cell surface protein receptor belonging to the TGF-β receptor superfamily (located on chromosome 2q31)
- BMP-BMPRII signaling plays an important role in embryogenesis, apoptosis, cell proliferation and differentiation.
- In vascular smooth muscles normal BMPR2 signalling causes inhibition of proliferation and favour apoptosis, thereby protecting the vessels from narrowing and development of hypertension
- Primary pulmonary hypertension is believed to be caused by a mutation in the gene coding for the BMPR II signaling pathway (PPH-1 gene/BMPRII gene)
- ***Mutation in the BMPR II gene (PPH-1gene) predisposes the cells to undergo proliferation rather than apoptosis and results in development of pulmonary hypertension.***




**366. Answer is D (↑ Pulmonary wedge pressure):** *Internal Medicine 5th/293*

***↑ pulomary wedge pressure is not a feature of Precapillary Pulmonary hypertension.***

*In precapillary pulmonary hypertension the abnormality that leads to elevated pulmonary pressure is located in the pulmonary artery or arterioles. The Left atrial pressure or Pulmonary capillary wedge pressure is essentially normal.*

| Features | Precapillary | Passive (Post-capillary) |
|---|---|---|
| Pathophysiology | Abnormality that leads to elevated pulmonary artery pressure is located in the pulmoanry artery or arterioles. | Abnormalities that lead to elevated pulmonary artery pressure are located beyond the pulmonary arteries. These are caused by diseases that lead to increased pulmonary venous pressure that in turn produces secondary elevation in pulmonary arterial pressure. |
| Pulmonary artery mean pressure | ↑/↑↑ | ↑ |
| ***Left Atrial Pressure (PCWP)*** | ***Normal*** | ↑ |
| PA left Atrial Pressure Gradient | > 12mm | <12mm Hg |
| Conditions/Causes | • *Primary pulmonary hypertension*<br>• *Disorders of ventilation*<br>• *Congenital heart disease with pulmonary vascular disease*<br>• *Pulmonary embolism*<br>• *Schistosmiasis*<br>• *Collagen vascular disease*<br>• *Pulmonary vasculitis*<br>• *Sickle hemoglobinopathies*<br>• *Portal hypertension*<br>• *Ingestion of drugs and herbal remedies* | • *Left ventricular failure*<br>• *Mitral valve disease*<br>• *Cor triatriatum*<br>• *Obstruction of major pulmonary veins*<br>• *Congenital pulmonary vein stenosis*<br>• *Left atrial myxoma or thrombosis* |

**367. Answer is A (Mitral stenosis):** *Internal Medicine 5th/293*

***Mitral stenosis is a cause of post-capillary pulmonary hypertension or passive pulmonary hypertension.***

**Causes of pulmonary hypertension:**

Precapillary pulmonary hypertension

- ***Primary pulmonary hypertension***
- *Disorders of ventilation*
- *Congenital heart disease with pulmonary vascular disease*
- ***Pulmonary embolism***
- *Schistosmiasis*
- *Collagen vascular disease*
- ***Pulmonary vasculitis***
- *Sickle hemoglobinopathies*
- *Portal hypertension*
- *Ingestion of drugs and herbal remedies*

Passive (Post-capillary) pulmonary hypertension

- *Left ventricular failure*
- ***Mitral valve disease***
- *Cor triatriatum*
- *Obstruction of major pulmonary veins*
- *Congenital pulmonary vein stenosis*
- *Left atrial myxoma or thrombosis*

Reactive pulmonary hypertension

- *Some patients with mitral valve disease*
- *Rarely, other cause of pulmonary venous hypertension, including pulmonary veno-occlusive disease*

**368. Answer is A (Hyperventilation):** Harrison 18th/p 2078, 2080 *Harrisons 17th/1577,1579*

***Pulmonary hypertension may be caused by hypoventilation but not by hyperventilation.***

*Chronic exposure to high altitude sleep disordered breathing due to obesity and anorexic agents including fenfluramine are known causes of pulmonary hypertension.*

Clinical Classification of Pulmonary Hypertension

1. **Pulmonary arterial hypertension (PAH)**
   - Idiopathic (IPAH)(formerly PPH)
   - Familial (FPAH)
   - Associated with (APAH)
     - *Collagen vascular disease*
     - *Congenital systemic-to-pulmonary shunts*
     - *Portal hypertension*
     - *HIV infection*
     - *Drugs and toxins (including fenfluramine)*
     - *Other (thyroid disorders, glycogen storage disease, Gaucher disease, hereditary hemorrhagic telangiectasia, hemoglobinopathies, myeloproliferative, disorders, splenectomy)*
   - Associated with significant venous or capillary involvement
     - *Pulmonary veno-occlusive disease (PVOD)*
     - *Pulmonary capillary hemangiomatosis (PCH)*
     - *Persistent pulmonary hypertension of the newborn*
2. **Pulmonary hypertension with left heart disease**
   - *Left-sided atrial or ventricular heart disease*
   - *Left-sided valvular heart disease*
3. **Pulmonary hypertension associated with lung diseases and/or hypoxemia**
   - *Chronic obstructive pulmonary disease*
   - *Interstitial lung disease*
   - ***Sleep-disordered breathing***
   - *Alveolar hypoventilation disorders*
   - ***Chronic exposure to high altitude***
   - *Developmental abnormalities*
4. **Pulmonary hypertension due to chronic thrombotic and/or embolic disease**
   - *Thromboembolic obstruction of proximal pulmonary arteries*
   - *Thromboembolic obstruction of distal pulmonary arteries*
   - *Nonthombotic pulmonary embolism (tumor, parasites, foreign material)*
5. **Miscellaneous**
   *Sarcoidosis, histiocytosis X, lymphangiomatosis, compression of pulmonary vessels (adenopathy, tumor, fibrosing mediastinitis)*

*A causal relationship has been established between exposure to several anorexigens including aminorex and the **fenfluramines** and the development of PAH-Harrison*

**369. Answer is D (Argemone mexicana poisoning):** Harrison 18th/p 2082 *Reference with text*

***Argemone mexicana poisoning has not been mentioned as a cause for pulmonary hypertension. It is the single best answer of exclusion.***

**Toxic oil syndrome is associated with pulmonary Hypertension** *(Goldrank's Toxicological Emergencies 7th/25)*
Toxic oil syndrome also called toxic epidemic syndrome is a multi system disorder characterized by pneumonitis, eosinophilia, ***pulmonary hypertension***, scleroderma like feature and neuromuscular changes
Toxic oil syndrome has first observed as an epidemic in spain due to consumption of 'Rapeseed oil' as cooking oil.

**Sickle cell anemia is associated with pulmonary hypertension(H17th/1581)**
*Cardiovascular abnormalities including pulmonary hypertension are prominent abnormalities in the clinical spectrum of sickle cell disease-H17th/1581*

**Systemic sclerosis is associated with pulmonary hypertension**
*All collagen vascular diseases including systemic sclerosis may be associated with pulmonary hypertension.(H17th/1579)*

**370. Answer is D (Bronchoconstriction):** Harrison 18th/p 2081 *Harrison 17th/1580*

***Bronchoconstriction is not a cause for Pulmonary Hypertension***

**Pulmonary Hypertension in COPD has been attributed to multiple factors including:**

- ***Hypoxia***
- ***Pulmonary vasoconstriction (secondary to hypoxia)***
- *Acidemia*
- *Hypercapnia*
- *Mechanical effect of **high lung volume** on pulmonary vessels*
- *Loss of small vessels in vascular bed*
- *Regions of emphysematous lung destruction*

## Aortic Dissection

**371. Answer is A (Acute Aortic dissection):** *Harrison 16th/1483; API 7th/512; Harrison 17th/1565, 1566; 18th/ 2064*

*Chest pain radiating to the back and interscapular region, with shock in presence of risk factors such as hypertension suggest a diagnosis of acute aortic dissection. Loss of pulses occurs when vessel orifices are obstructed by mobile intimal flaps and pulses may well be preserved if such obstruction does not occur. A pleural effusion (left sided) may also be present. – Harrison & API*

- A ***pleural effusion*** (usually left sided) may also be present. The effusion is typically serosanguinous and does not indicate rupture unless accompanied by hypotension and falling haematocrit. – *Harrison 16th*
- ***Pain*** may be localized to the front back of the chest, often in the interscapular region and typically migrates with propagation of the lesion.
  'Severe pain from onset differentiates it from myocardial infarction' – *API7th/512*
  *Sudden onset pain, severe, tearing associated with diaphoresis.*
- ***Pulse deficits*** may be produced obstruction of the branches by compression of the true lumen by distended false lumen or by obstruction of the vessels orfice by mobile intimal flag. Peripheral pulses thus may be normal if the pathologic process does not compromise their orifices.
- ***Risk factor*** include old age (50-70 yrs), ***hypertension***, females sex, pregnancy bicuspid or unicuspid aortic valve, Noonan or Turner's syndrome, cocaine abuse or connective tissue disorders such as Marfan's Ehler's Danlos syndrome, or arteritis such as Takayasu's or giant cell arteritis.

**372. Answer is C (MR):** Harrison 18th/p 2064 *Harrison 17th/1566*

*Mitral Regurgitation is not a feature of Aortic dissection*

**Aortic Regurgitation and Pericardial Tamponade may be seen in proximal dissection**

*Hemopericardium and cardiac tamponade may complicate a dissection involving the ascending aorta (type A lesion with retrograde dissection): H17th/1566*

*Acute Aortic Regurgitation (AR) is an important and common complication of proximal dissection – H 17th/1566*

**Acute Myocardial Ischemia may be associated with Aortic dissection**

*'Bowel Ischemia, hematuria and myocardial Ischemia have all benn observed with Aortic dissection' – H 17th/1566*

**373. Answer is C (In Ist trimester pregnancy):** *Harrison 17th/1656*

*Aortic dissection is predisposed during Third trimester of pregnancy and not during the first trimester of pregnancy*

Risk factors / Predisposing factors for Aortic Dissection

- ***Systemic Hypertension and cystic medial necrosis***
- Connective Tissue Disorders
  - ***Marfan's Syndrome***
  - Ehler's Danlos Syndrome
- Inflammatory Aortititis
  - ***Takayasu arteritis***
  - Giant cell arteritis
- Congenital Aortic Valve abnormalities
  - Bicuspid Aortic Valve
- ***Coarctation of Aorta***
- Aortic trauma
- ***Third trimester of pregnancy***

**374. Answer is B and D (Diazoxide and Hydralazine):** Harrison 18th/p 2064 *Harrison 17th/1566*

*Diazoxide and Hydralazine are direct vasodilators and isolated use of direct vasodilators is contraindicated in Aortic dissection because these agents may propagate dissection by increasing hydraulic shear.*

*'Isolated use of direct vasodilators such as diazoxide and hydralazine is contraindicated because these agents can increase hydraulic shear and may propogate dissection'- H17th/1566*

**Agents recommended in treatment of Aortic Dissection**

- ***Beta Adrenergic blockers (propanolol/metoprolols/esmolol) intravenously***
- ***Sodium Nitroprusside***
- ***Labetolol (may be used)***
- *Calcium channel blockers (Verepamil/Diltiazam)*
  (May be used if Beta blockers or Nitroprusside cannot be employed)

## Cardiopulmonary Resuscitation

**375. Answer is C (Compression- Airway – Breathing (C-A-B)):** *AHA 2010 Guidelines*

***The major Highlight of the 2010 AHA Guidelines for CPR is the Change from "A-B-C" to "C-A-B"***
*The newest development in the 2010 AHA Guidelines for CPR and ECC is a change in the basic life support (BLS) sequence of steps from "A-B-C" (Airway, Breathing, Chest compressions) to "C-A-B" (Chest compressions, Airway, Breathing) for adults and paediatric patients (children and infants, excluding new-borns)*

**Summary of Key BLS Components for Adults, Children, and Infants**
(Excluding the new-born, in whom the etiology of an arrest is nearly always asphyxia)

| Component | Recommendations | | |
|---|---|---|---|
| | Adults | Children | Infants |
| | Unresponsive (for all ages) | | |
| Recognition | No breathing or no normal breathing (i.e. Only gasping ) | No breathing or only gasping | |
| | No pulse palpated within 10 seconds for all ages (HCP only) | | |
| **CPR sequence** | **C-A-B** | | |
| **Compression rate** | **At least 100/min** | | |
| Compression depth | At least 2 inches (5cm) | At least 1/3 AP diameter<br>About 2 inches (5cm) | At least 1/3 AP diameter<br>About $1^{1}/_{2}$ inches (4cm ) |
| Chest wall recoil | Allow complete recoil between compressions<br>HCP s rotate compressors every 2minutes | | |
| Compression interruptions | Minimize interruptions in chest compressions<br>Attempt to limit interruptions to < 10 seconds | | |
| Airway | Head tilt- chin lift<br>(If HCP suspects trauma use Jaw Thrust) | | |
| Compression-to –ventilation ratio (until advanced airway placed) | 3:2<br>1 or 2 rescuers | 30;2 Single rescuer<br>15:2 2HCP rescuers | |
| Ventilations; when rescuer untrained or trained and not proficient | Compressions only | | |
| Ventilations with advanced airway (HCP) | 1 breath every 6-8 seconds (8-10 breaths/min)<br>Asynchronous with chest compressions<br>about 1 second per breath<br>visible chest rise | | |
| Defibrillation | Attach and use AED as soon as available.<br>Minimize interruptions in chest compressions before and after shock;<br>Resume CPR beginning with compressions immediately after each shock. | | |

AED, automated external defibrillator; AP. Anterior-posterior; CPR, cardiopulmonary resuscitation; HCP, healthcare provider. .

**376. Answer is B (Emphasis on "Look, Listen, and Feel' for Breathing):** *AHA Guidelines; Refer : ACLS Comparison Sheet*

*According to the new 2010 AHA Guidelines "Look, listen, and feel" has been removed from the CPR sequence.*

| Key issues and major changes in the 2010 AHA Guidelines for CPR for lay rescuer in adult CPR include: (Emphasis on Chest Compressions) |
|---|
| • Change in CPR Sequence to C-A-B Rather than A-B-C<br>• Chest Compression Rate of at least 100 per Minute<br>• Chest Compression Depth to at least 2 inches (5 cm)<br>• Elimination of "Look, Listen, and Feel for Breathing" |

**377. Answer is A (Airway – Breathing – Compression (A-B-C)):** *AHA Guidelines*

***The A-B-C (Airway – Breathing – Compression) sequence is still retained for neonates since cardiac arrests in neonates are nearly always from asphyxia.***

The major Highlight of the 2010 AHA Guidelines for CPR is the Change from "A-B-C" to "C-A-B". The newest development in the 2010 AHA Guidelines for CPR and ECC is a change in the basic life support (BLS) sequence of steps from "A-B-C" (Airway, Breathing, Chest compressions) to "C-A-B" (Chest compressions, Airway, Breathing) for adults and paediatric patients (children and infants, excluding new-borns). ***However the A-B-C (Airway – Breathing – Compression) sequence is still retained for neonates since cardiac arrests in neonates are nearly always from asphyxia.***

**378. Answer is A (Amiodarone):** *Cardiovascular Therapeutics: A Companion to Braunwald's Heart Disease By Elliott M. Antman 4th/ 415*

***Amiodarone is the preferred antiarrhythmic agent for resuscitation in a patient with cardiac arrest.*** *Amiodarone is the preferred antiarrhythmic agent for resuscitation, In patients with VF/VT that does not respond to CPR, defibrillation, and vasopressor therapy.*

Amiodarone is the first-line antiarrhythmic agent given during cardiac arrest because it has been clinically demonstrated to improve the rate of ROSC (Return of Spontaneous Circulation) and hospital admission in adults with refractory VF/pulseless VT. Amiodarone should be considered when VF/VT is unresponsive to CPR, defibrillation, and vasopressor therapy. If Amiodarone is unavailable, Lidocaine may be considered, but in clinical studies Lidocaine has not been demonstrated to improve rates of ROSC and hospital admission compared with Amiodarone. Procainamide may be used for stable wide QRS Tachycardia but not for pulseless cardiac arrest and must be avoided in Torsades De Pointes. Magnesium sulphate should be considered only for Torsades de pointes associated with a long QT interval

**379. Answer is C (Atropine):** *'Critical Care Medicine: Principles of Diagnosis and Management in the Adult' edited by Joseph E. Parrillo, R. Phillip Dellinger 4th / 6; Cardiovascular Therapeutics: A Companion to Braunwald's Heart Disease By Elliott M. Antman 4th/ 415*

***The use of Atropine for cardiac arrest (PEA / Asystole) has been removed from the ACLS 2010 Guidelines / Algorithm due to lack of any evidence showing therapeutic benefit.***

The primary Pharmacological agents included in the ACLS Algorithm for management of cardiac arrest include Epinephrine, Vasopressin and Amiodarone.

- The primary goal of pharmacologic therapy is to assist the achievement and maintenance of spontaneous circulation.
- The mainstay of pharmacologic interventions is vasopressor agents. **Epinephrine** (1mg) is recommended by IV or via the intraosseous (IO) route every 3 to 5 minutes during resuscitative efforts until spontaneous circulation is restored. If IV/IO access cannot be established, epinephrine can be administered via an endotracheal tube at a higher dose (2 to 2.5mg).

  **Vasopressin** (40 mg iv/IO) could be substituted for the first or second dose of epinephrine if desired.
- The preferred antiarrhythmic agent for resuscitation is Amiodarone. **Amiodarone** is recommended in patients with VF/VT that does not respond to CPR, defibrillation, and vasopressor therapy. (first dose; 300mg IV/IO; second dose; 150mg IV/10).

**Drug therapy**

- **Epinephrine IV/IO Dose;** 1 mg every 3-5 minutes
- **Vasopressin IV/IO Dose;** 40 units can replace first or second dose of epinephrine
- **Amiodarone iv/IO Dose;** First dose; 300 mg bolus second dose; 150 mg

*Lidocaine is not part of the ACLS 2010 Algorithm but may be used. The AHA recommends its administration after epinephrine; vasopressin and Amiodarone have been tried. But in clinical studies Lidocaine has not been demonstrated to improve rates of ROSC and hospital admission*

***It should be noted that***
***The use of atropine for PEA/Asystole was recently removed from the ACLS algorithm.***
*Evidence is insufficient to recommend routine administration of sodium bicarbonate during resuscitation.*

*compared with Amiodarone. It is given in a bolus of 1mg/kg. A second loading dose of 1 mg/kg can be given in 10-15 minutes after the first one.*

ACLS: Pharmacological agents

| Medications that have been changed | Medications that have remained unchanged |
|---|---|
| • Atropine: deleted from pulseless arrest algorithm<br>• Sodium Bicarbonate: Routine use not recommended<br>• Calcium: Routine administration for treatment of cardiac arrest not recommended | • Epinephrine: dose, interval unchanged<br>• Vasopressin: dose, use unchanged<br>• Amiodarone: dose, indications unchanged<br>• Lidocaine: dose, indications unchanged |

**380. Answer is A (Ventricular Tachycardia)**: Harrison 18th/p 2239, 2244 *Harrisons 17th/1712,1708*

***Defibrillation is indicated when cardiac arrest occurs secondary to ventricular fibrillation or pulseless ventricular tachycardia (shockable rhythms)***

**ECG Rhythms in Cardiac Arrest**

| Shockable Rhythms<br>**(Urgent Drefibrillation is required)** | Non shockable Rhythms<br>**(Defibrillation is not indicated)** |
|---|---|
| • Ventricular Fibrillation<br>• Ventricular Tachycardia (Pulseless) | • Persistant/ Sustained Bradyarrhythmia<br>• Asystole<br>• Pulseless Electrical Activity (PEA) (Electromechanical dissociation) |

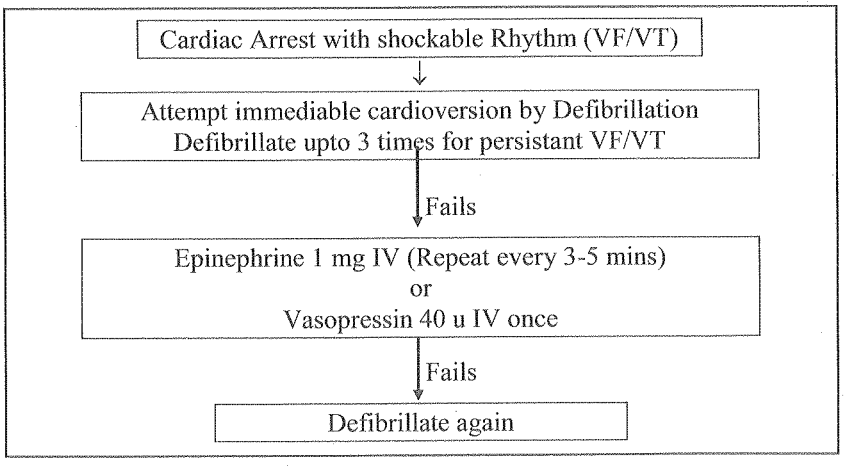
*Electromechanical dissociation is the former terminology for PEA*

**381. Answer is C (Adrenaline is given if cardioversion fails):** Harrison 18th/p 2239, 2243, 2244 *Harrisons 17th/1708,1711,1712; Harrisons 16th/1622,1623*

***During cardiopulmonary rescuscitation (CPR), administration of Adrenaline is recommended only after attempts at cardioversion fail.***

**Adrenaline (Epinephrine) is given if cardioversion fails**

Cardioversion is a brief procedure where an electric shock is given to the heart to convert an abnormal heart rhythm back to a normal rhythm (Defibrillation)
Cardioversion/Defibrillation is recommended as the immediate step during cardiopulmonary resuscitation.
*Adrenalene/Epinerphrine is recommended only after failed defibrillation/cardioversion*
*'Epinephrine 1 mg intravenously is given after failed defibrillation'* –H17th/1712



**Most common presentation on ECG is ventricular fibrillation (VF) and not Asystole (H17th/1708)**

*'The most common electrical mechanism for true cardiac arrest is ventricular fibrillation (VF) Which is responsible for 65 to 80% of cardiac arrest'– Harrison*

*'Asystole, Pulseless Electrical Activity and Severe Bradyarrhythmias cause the remaining 20 to 30%'* - Harrison

**Recommended compression to ventilation ratio is 30:2 and not 5:1 (ACLS guidelines)**

The current recommendations require the lungs to be inflated twice in succession every 30 (Harrisons 17th/1712)

| Traditional Recommendations for compression to ventilation ratio | Recent Recommendations (ACLS) guidelines) for compression to ventilation ratio |
|---|---|
| 15:2 for one person CPR<br>5:1 for more than one person CPR<br>This was later changed to 15:2 in all situation | 30:2 for one person CPR<br>When 2 rescuers are present the<br>- Compressing rescuer should deliver 100 Compressions per minute continuously without pauses for ventilation<br>- The rescuer delivering the ventilations should give 8-10 breaths per minute |

**Calcium gluconate is not recommended for routine administration (H17th/1712)**

Intravenous calcium gluconate is no longer considered necessary or safe for routine administration
It is now only recommended for certain specific indications

| Indications for calcium gluconate administration |
|---|
| *Acute hyperkalemia (Known to be the triggering event for resistant VF)* |
| *Hypocalcemia*[Q] |
| *Patients who have received toxic doses of calcium channel antagonisits*[Q] |

**382. Answer is A & B (Atropine) & (External cardiac pacing):** Harrison 18th/p 2239, 2244 *Harrison's 17th/-1712, 1708, Advanced cardiac Life support (ACLS) Manual Irwin & Rippe's Intensive care medicine 6th/332*

***Atropine and External cardiac pacing may be used in cardiac arrest following non shockable rhythms like Asystole but they have no role in the management of cardiac arrest with shockable rhythms like VF***

**Role of vasopressin**

Vasopressin has recently emerged as a potential agent for use in patients with cardiac arrest unresponsive to epinephrine and defibrillation 'Revised guidelines for ACLS recommend vasopressin as an alternative to epinephrine for the treatment of adult shock refractory ventricular fibrillations'- *Irwin & Rippe's Intensive care medicine 6th/-332*

**383. Answer is C (Adrenaline is given if cardioversion fails):** Harrison 18th/p 2244 *Harrisons 17th/1711, 1712*

*Cardioversion is a brief procedure where an electric shock is given to the heart to convert an abnormal heart rhythm back to a normal rhythm.*

*Cardioversion / Defibrillation is recommended as the immediate step during cardiopulmonary resuscitation. Adrenaline (Epinephrine) is recommended only after failed defibrillation / cardioversion*

*'Epinephrine 1mg intravenously is given after failed defibrillation / cardioversion'* - *Harrison*

**384. Answer is B (Ventricular fibrillation):** *Oxford handbook of Medicine 5th/712.*

*Asynchronous cardioversion is the most reliable method for terminating V.F.*

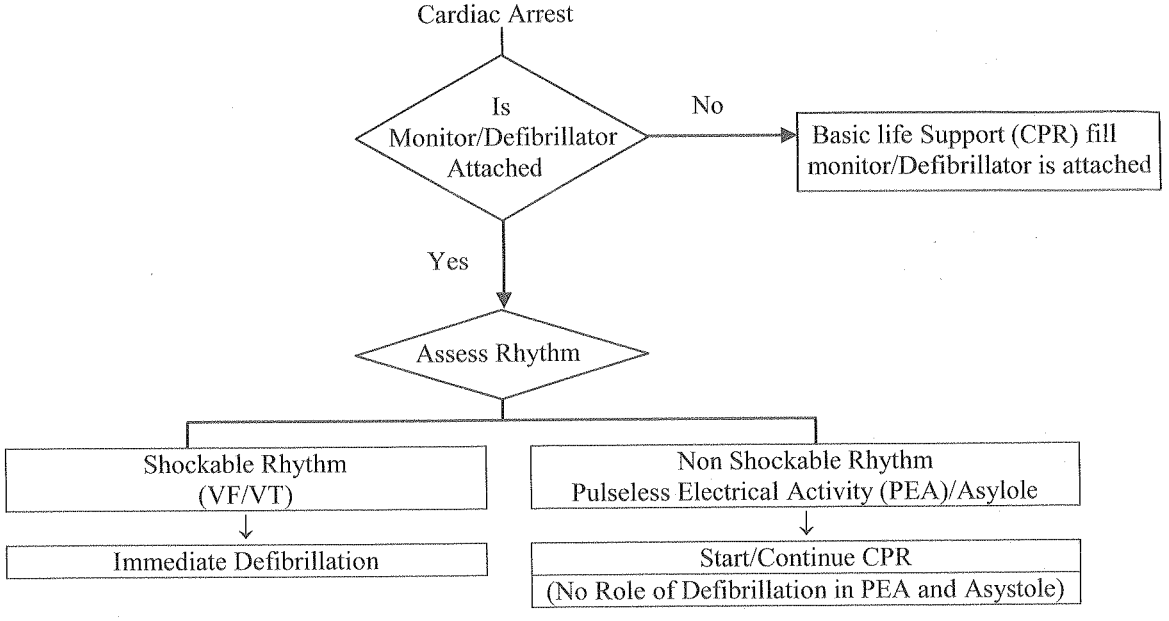
***Electrical cardioversion and defibrillation are the most reliable methods for termination of arrhythmias.*** These methods depolarize all or at least a large portion of excitable myocardium in a near homogenous fashion. Thereby interrupting reequitant rhythms.

**Cardioversion/defibrillation** *(Oxford handbook 5th/712)*

| *Atrial fibrillation (fast)*<br>*Supraventricular tachycardia* | *Ventricular fibrillation* |
|---|---|
| ***Synchronized*** cardioversion | ***Asynchronized*** cardioversion |
| For these conditions it is necessary to synchronize the shock of the 'R' wave of the ECG (by pressing 'SYNC' button on the machine). This ensures that the shock does not initiate a ventricular arrhythmia | If the 'SYNC' mode is engaged in ventricular fibrillation the defibrillator will not discharge. |

**385. Answer is C (Defibrillation ):** Harrison 18th/p 2244 *Harrisons 17th/1712*

***Immediate Defibrillation is the resuscitative measure of choice in all patients in cardiac arrest due to ventricular fibrillation on ventricular tachycardia (Shockable Rhythms) irrespective of the cause.***




**Note**

- *The speed with which defibrillation /cardioversion is carried out is the most important determinant for the success of resuscitation.*
- *Defibrillation should be carried out immediately (as early as possible), even before intubation or insertion of an intravenous device.*

**386. Answer is A (Ventricular Tachycardia):** Harrison 18th/p 2243 *Harrisons 17th/1711*

***The outcome after cardiac arrest is best if the mechanism is ventricular tachycardia- Harrisons 17th/1711***

| **Outcome after cardiac arrest in decreasing order of success** |
|---|
| Ventricular tachycardia (Best) |
| Ventricular fibrillation (Second Best) |
| Asystole |
| Pulseless Electrical activity (Electromechanical dissociation) |

**387. Answer is B (Hyperkalemia) :** Harrison 18th/p 2244 *Harrisons 17th/1712*

***Calcium gluconate is indicated in Hyperkalemia and not in hypokalemia***

**Calcium gluconate in Cardiopulmonary Resuscitation**

Intravenous calcium gluconate is no longer considered necessary or safe for routine administration during cardiopulmonary resusciatation

Calcium gluconate may however be recommended for certain specific indications during CPR These include

Indications for Intervenous calcium gluconate during CPR

*Hyperkalemia (When Acute hyperkalemia is known to be the triggering event for resistant VF)* Q
*Hypocalcemia* Q
*Calcium channel anatagonist toxity* Q

## Cardiac Tumors

**388. Answer is A (Myxoma) :** *Harrison 14th/1341, 15th/1373;Robbins 6th/589*

*The most common primary cardiac tumor is Myxoma.*

Remember

- The most frequent cardiac tumor for all age groups is - ***Metastasis***.
- The most frequent primary cardiac tumor for age groups is - ***Myxoma***.
- The most frequent primary cardiac tumor in infants and children is - ***Rhabdomyoma***.

**389. Answer is A (Myxoma):** *Repeat*

*The commonest tumor of myocardium is a myxoma.*

**390. Answer is A (Most common in Left Atrium):** *Harrison 14th/ 1341; 15th/ 1373; 16th/ 1421; 17th/ 1495, 1496*

*Cardiac Myxomas are usually located in the atria, most common in the left.*

**Cardiac myxomas :**

- Are the most common type of primary cardiac tumors. Q
- Occur at *all ages* and show ***no sex preference (mixes equally with both sexes)*** Q
- ***Most cardiac myxomas are sporadic***, while some may be familial

| Sporadic myxomas : | Familial myxomas : |
|---|---|
| • Are solitary Q | • Are multiple Q |
| • Located in Atria, most commonly in the left Q | • More likely to have post op recurrence Q |
| • Unlikely to have post-op recurrence Q | |
| • Occur in younger individuals Q | |

- ***Myxomas are benign tumors and therefore distant metastasis are not seen.*** Q

**391. Answer is D (Most myxomas are fmilial):** *Previous question*

*Most cardiac myxomas are sporadic while some may be familial.*

**392. Answer is C (Hypertension):** *Harrison 14th/ 1341, 16th/ 1421; 17th/ 1495, 1496; Repeat* Harrison 18th/p 1979

*All options other than hypertension are mentioned as features of atrial myxoma.*

**Atrial Myxoma :** Clinical Presentation:

Presentation is highly dependent on position of tumour and hence it is intermittent and sudden in onset.
*(as a result of changes in tumor position with gravity).*

| Cardiac signs and symptoms | Non cardiac signs and symptoms |
|---|---|
| - Picture of Mitral valve disease | - **Peripheral or pulmonary emboli** Q |
| - Characterised by low pitched sound– 'tumor plop' Q (audible during early or mid diastole). | - **Fever** : Prolonged pyrexia of unknown origin Q |
| | - **Clubbing** Q |
| | - Raynaud's Phenomenon Q |
| | - Anemia/polycythemia or thrombocytopenia / thrombocytosis Leucocytosis |
| | - Elevated ESR Q |
| | - Rash Q |
| | - Weight loss, cachexia, malaise, arthralgia |

**393. Answer is A (Commonest site is LA):** *Harrison 14th/ 1341; 15th/ 1373; 16th/ 1421; 17th/ 1495, 1496; 18th/p 1979*

*Cardiac Myxomas are usually located in the atria, most common in the left.*

**Cardiac myxomas :**

- Are the most common type of primary cardiac tumors. Q

- Occur at *all ages* and show *no sex preference* (mixes equally with both sexes) Q
- Most cardiac myxomas are sporadic, while some may be familial

| Sporadic myxomas : | Familial myxomas : |
|---|---|
| • Are solitary Q<br>• Located in Atria, most commonly in the left Q<br>• Unlikely to have post-op recurrence Q<br>• Occur in younger individuals Q | • Are multiple Q<br>• More likely to have post op recurrence Q |

- *Myxomas are benign tumors and therefore distant metastasis are not seen.* Q

**394. Answer is C (Left atrial myxoma):** *Harrison 15th/ 1279; 16th/1421; Harrison 17th/ 1496* Harrison 18th/p 1979

*An increased gradient during diastole is suggestive of an obstructive lesion between Left atrium and Left ventricle that is not allowing pressures to normalize between the atria and ventricle such as atrial myxoma.*

*Pulmonary artery wedge pressure* represents Left atrial pressure.

*Left ventricular end diastolic pressure* represents Left ventricular pressure.

**Gradient between Left atrial pressure (PCWP) and Left ventricular pressure during diastole:**

***Normally*** there is no gradient during diastole as both pressures are equal.

***An increased gradient during diastole*** is suggestive of an obstructive lesion between Left atrium and Left ventricle that is not allowing pressures to normalize between the atria and ventricle.

*This may thus be seen in obstructive lesions between Left atria and ventricle such as* :

1. Mitral stenosis
2. Atrial myxomas

## Rheumatic Fever

**395. Answer is C (Fever):** *Harrison 16th / 1978; Harrison 17th/2095* Harrison 18th/p 2755

*Fever is a Minor Jones Criteria for diagnosis of Rheumatic fever.*

**The Jones Criteria**

Jones criteria were first proposed in 1944.

The most recent modification of the Jones criteria was published in 1992 and these were termed updated Jones criteria.

**Updated Jones Criteria for Rheumatic fever**

| Major Criteria | Minor Criteria |
|---|---|
| • Carditis<br>• Migratory polyarthritis<br>• Sydenham's chorea<br>• Subcutaneous nodules<br>• Erythema marginatum | • ***Fever (clinical)***<br>• Arthralgia (clinical)<br>• Elevated acute phase reactions (LAB)<br>• Prolonged PR internal (LAB / ECG) |

| Essential Criteria |
|---|
| Supporting evidence of recent group A streptococcal infection.<br>• Positive throat culture or rapid antigen detection test and / or<br>• Elevated or increasing streptococcal antibody test. |

***To fulfill the Jones Criteria,***
***Two major criteria or One major criteria And Two minor criteria***
***PLUS***
***Essential criteria are required.***

**396. Answer is C (Fever):** *Harrison 16th / 1978*

*Fever is a Minor Jones Criteria for diagnosis of Rheumatic fever.*

**397. Answer is D (High ESR):** Harrison 18th/p 2755 *Harrison's 17th/2095*

***Elevated (High) ESR is a minor criterion and not a major criterion (Jones criteria)***

| World Health Criteria for the diagnosis of Rheumatic fever and rheumatic heart disease | |
|---|---|
| **Major manifestations** | • *Carditis*<br>• *Polyarthritis*<br>• *Chorea*<br>• *Erythema marginatum*<br>• *Subcutaneous nodules* |
| **Minor manifestations** | • Clinical: fever, polyarthralgia<br>• Laboratory: elevated erythrocyte sedimentation rate or leukocyte count<br>• Electrocardiogram: prolonged P-R interval<br>*@1992 Revised Jones criteria do not include elevated leucocyte count as a laboratory minor manifestation (but do include elevated C-reactive protein)* |
| ***Supporting evidence of a preceding streptococcal infection within the last 45 days*** | • Elevated or rising anti-streptolysin O or other streptococcal antibody, or<br>• A positive throat culture, or<br>• Rapid antigen test for group A streptococcus, or<br>• Recent scarlet fever<br>*@1992 Revised Jones criteria do not include recent scarlet fever as supporting evidence of a recent streptococcal infection* |

| Diagnostic Categories | Criteria |
|---|---|
| ***Primary episode of rheumatic fever*** | *Two major or one major two minor manifestations plus evidence of preceding group A streptococcal infection* |
| ***Recurrent attack of rheumatic fever in a patient without established rheumatic heart disease*** | *Two major or one minor manifestations plus evidence of preceding group A streptococcal infection* |
| ***Recurrent attack of rheumatic fever in a patient with established rheumatic heart disease*** | *Two minor manifestations plus evidence of preceding group A streptococcal infection* |

**398. Answer is A (Migratory Polyarthralgia):** *Harrison 18th/ 2753*

***Major Joint involvement criteria in Acute Rheumatic Fever are Migratory Polyarthritis*** *(Not Polyarthralgia). The typical polyarthritis is migratory moving from one joint to another over a period of hours*

**399. Answer is A, C and E (Chorea, Arthritis and carditis):** *Harrisons 17th / 2095; Harrisons 16th / 1978; Nelsons 18th /1141* Harrison 18th/p 2755

*Chorea, Arthritis and Carditis are major criteria for diagnosis of Rheumatic fever*
*Fever is a minor criteria*
*Erythema Marginatum is a major criteria and not Erythema nodosum.*

**400. Answer is A, C, E (Chrorea, Arthritis, Carditis) :** *Refer text below*

*Chorea, Arthritis and Carditis are major criteria for diagnosis of Acute Rheumatic fever*
*Acute Rheumatic fever is associated with Erythema marginatum and not Erythema nodosum*
*Acute Rheumtic fever is associated with Antecedent Group A streptococcal infection and not with antecedent α - hemolytic streptococcal infection.*

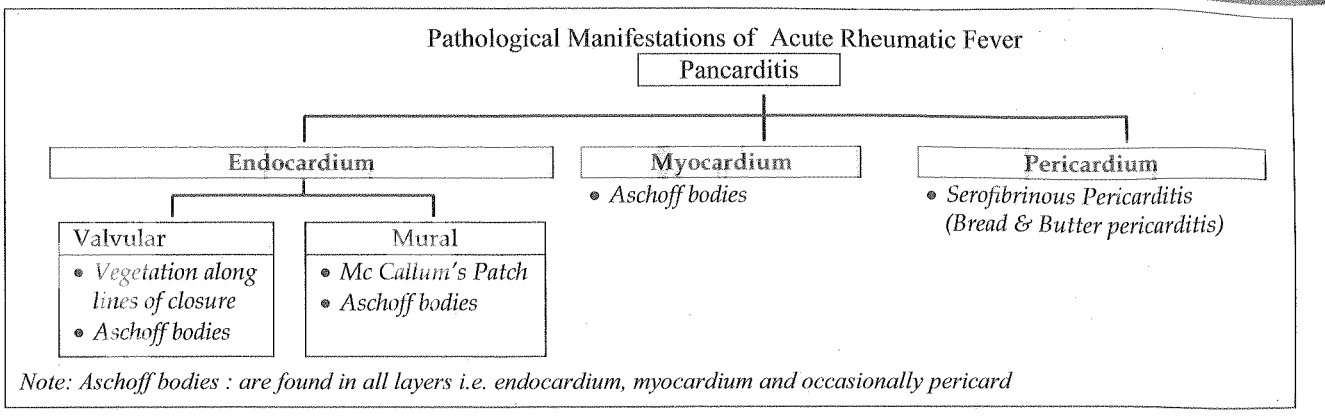
**401. Answer is D (Pancarditis) :** *Robbins 7th /593*

*Rheumatic fever is characterized by Pancarditis.*

*During Acute Rheumatic fever, diffuse inflammation and Aschoff bodies may be found in any of the three layers of heart - pericardium, myocardium or endocardium, hence the lesion is called pancarditis. – Robbin's 7th/593*

**402. Answer is B (Rupture of Chordae tendinae) :** *Pathologic basis by Robbins 5th / 547; 6th/322*

*Rupture of chordae temdinae is not a feature of Acute rheumatic fever*




*Note: Aschoff bodies : are found in all layers i.e. endocardium, myocardium and occasionally pericard*

**403. Answer is A (Aschoff's nodule) :** *Robbins 5th / 549*

*"Aschoff's body is pathognomic of Rheumatic fever" - Robbins*

**Aschoff's bodies** *are focal inflammatory lesions, that may be found in any of the three layers of the heart - Pericardium, Myocardium and Endocardium, during acute Rheumatic fever.*

Aschoff bodies consist of foci of swollen eosinophillic collagen surrounded by

- Lymphocytes (primarily T cells)
- Occasional plasma cells
- Aschoff giant cells (macrophages of rheumatic fever)
- Antitschkow cells
  *(Antischkow cells are modified macrophages with abundant cytoplasm and central round to ovoid nuclei in which the chromatin is disposed in the central, slender wavy ribbon like pattern – caterpillar cells)*

**404. Answer is C (Rheumatic carditis):** *Robbins 7th/ 593; (Repeat)*

*Aschoff bodies are characteristic focal inflammatory lesions of acute rheumatic fever found in any of the three layers of the heart.*

*"Aschoff's body is pathognomic of Rheumatic fever" - Robbins*

**Aschoff bodies:**

- Aschoff bodies are focal inflammatory lesions seen during acute rheumatic fever
- During acute RF, Aschoff bodies may be found in any of the three layers of the heart – pericardium, myocardium and endocardium.
- *Aschoff's body is pathognomic of Rheumatic fever*

**405. Answer is B (Rheumatic endocarditis) :** *Harsh Mohan 4th / 304*

*Mac Callum's Patch is a feature of mural endocarditis in Rheumatic fever.*

**Mac Callum's Patch**

- '*Mc.Callum's patch*' is the region of endocardial surface *in the posterior wall*♀ of left atrium just above the posterior leaflet of mitral valve.
- It appears as a 'map like' area of thickened, roughened, and wrinkled part of endocardium.
- It is perhaps produced as a result of regurgitant jets.

**Rheumatic Endocarditis**

**Valvular lesion**
(Rheumatic valvular endocarditis)

**Mural lesion**
(Rheumatic mural endocarditis)

Involvement of Mural endocardium is in the form of ***"Mc.Callum's patch"*** ♀

**406. Answer is C (Communicable disease):** Harrison 18th/p 2752, 2753 *Harrison 17th/2092, 2093; Nelson 16th/ 806*

*Rheumatic fever is not a communicable disease. Rheumatic fever occurs as a result of immunological hypersensitivity to streptococcal antigens.*

- *Group A β hemolytic streptococii is the causative agent.*
- *The major risk factor for development of acute rheumatic fever is a group A streptococcal pharyngitis (upper respiratory tract infection).*
- *Group A streptococcal impetigo (slum infection) does not result in acute rheumatic fever.*
- *[Post streptococcal glomerulonephritis however may be caused following both, an upper respiratory tract infection as well as infection of slum.]*
- *Rheumatic fever is most frequently observed in the age group of 5-15 years.*
- *The incidence* of rheumatic fever has declined in developed countries while in developing countries (poor socioeconomic groups) it remains a significant problem.

**407. Answer is A (Chorea is aggrevated during pregnancy):** Harrison 18th/p 2754 *Harrisons 17th/2094 Recent advances in Pediatrics 23rd/12*
*The 5 minute Neurology Consult (2003) /394, Oxford textbook of Medicine 4th/1052: Nelsons 18th/1142.*

*Sydenham's chorea may be aggravated by pregnancy.*

*'Patient's with sydenham's chorea may have chorea during pregnancy (chorea gravidarum) and are at higher risk of chorea induced by phenytoin or oral contraceptives' - The 5- Minute Neurology consult (2003) /399*

*Sydenhom's chorea usually occurs in isolation and is not associated with arthritis usually. Subcutaneous nodules are typically non tender. Rheumatic fever is associated with Erythema marginatum and not Erythema multiforme*

Featues of Sydenham's chorea in Rheumatic Fever (10-15% of patients)

- *It usually occurs after a prolonged latent period after group A streptococcus*
- *It usually occurs in the absence of other manifestation (usually not associated with arthritis or carditis)*
- *It usually occurs in females*
- *Presents as rapid, jerkey, involuntary movements (choreiform movements) affecting predominantly the Head /Face and Upper limbs*
- *May be generalized or restricted to one side / asymmetrical*
- *Typical signs include*
  - *Milk maid Grip*
  - *Spooning of extended hands*
  - *Darting of the protruded tongue*
  - *Pronator signs*
- *Typically associated with excessive emotional lability and personality changes*
- *It is a self limiting condition and eventually resolves completely, usually within 6 weeks.*
- *Recurrence of chorea may be seen late after complete resolution*
  Factors inducing Recurrence
  - *Pregnancy (Chorea gravidorum)*
  - *Re infection with streptocossus / non specific infections*
  - *Use of oral contraceptives*

**408. Answer is A and D (Polyarthritis and MC valve involvement is Mitral):** Harrison 18th/p 2753, 2754, 2755
*Harrisons 17th/2093, 2094, Ghai 6th/376-378*

*Polyarthritis is a major criteria for diagnosis of RF.*
*Most common valve involved in Rheumatic carditis is mitral valve.*

*Erythema marginatum is a rare manifestation (<3% of patients) and almost never involves the face.*
*Acute Rheumatic fever is caused by Group A streptococcii and not alpha hemolytic streptococcii*

**Features of Erythema Marginatum**

- ***Erythema marginatum is rare (< 3% of patients with Acute Rheumatic fever)***
- *Erythema marginatum is charachteristic / classic rash of Acute Rheumatic fever (Rare but charachteristic)*
- ***Typically occurs on the trunk or the proximal limbs (Never on the Face)***
- *Appears as ring that extends contrifugally (marginatum) while the skin in the centre of the ring returns to normal*
- *Rash is evanescent, pink to red*
- *Rash is non pruiritic*
- ***Rash occurs commonly in assoication with carditis (usually occurs only in patients with carditis)***
- *Rash leaves no induration and no scarring.*

**409. Answer is D (usually associated with carditis) :** Harrison 18th/p 2754 *Harrisons 17th/2094; Nelson's 18th/1142; Mayo clinic Cardiology / 3rd /551*

*Erythema marginatum and sub cutaneous nodules are usually associated with carditis manifestation*
*Erythema marginatum is a rare (< 3%) manifestation of Acute Rheumatic fever. Rash is charachteristically non pruiritic and almost never involves the face.*

**410. Answer is A & C (Non tender; Present on extensor surfaces):** *Harrison 18th/2754; 17th/2094; Nelson's 18th/1142-43*

*Subcutaneosis nodules in Rheumatic fever are non tender and commonly located on extensor surfaces*

*These are a rare manifestation of Rheumatic fever and are commonly associated with carditis*

Features of Subcutaneous nodules in Rheumatic Fever

- *Rare manifestation (≤ 1% of patients with acute Rheumatic fever)*
- *Delayed manifestation (appearing 2-3 weeks after onset of disease)*
- *Located commonly along the extensor surfaces of tendons near bony prominences (particularly hands, feet, elbows, occiput / occasionally vertebra)*
- *Painless (Non tender)*
- *Mobile*
- *Small in size (0.5 – 2cm)*
- *Commonly assoicated with carditis*
- *Nodules last for just a few days to upto 3 weeks*

**411. Answer is A (Mitral Regurgitaion):** *Harrison 18th/p 2753 Harrisons 17th/2094*

*The most common valvular lesion is Acute Rheumative fever a mitral Regurgitation.*
*Mitral valve is the most commonly involved valve in Rheumatic fever*
*The most common valvular abnormality secondary to Rheumatic fever is mitral stenosis, however mitral stenosis is seen as a chronic manifestation of Rheumatic heart disease and is not a manifestation of Acute Rheumatic fever*
***Early valvular damage leads to mitral regurgitation which is the commonet lesion seen in Acute Rheumatic fever.***

## Congenital Heart Disease

### General:

**412. Answer is D (Multifactorial):** Harrison 18th/p 1920 *Harrison 17th/1458; Robbins 6th/ 592; Robbins 5th/ 571*

*Congenital heart disease is the most common type of heart disease among children.* Q
*Multifactorial Genetic and Environmental factors account for the majority of cases.* – *Robbins*

***Remember :***

| Extracardiac Lesion | Most likely congenital cardiac lesion |
|---|---|
| *Down's syndrome* Q | ASD Q of endocardial cushion type |
| *Turner's Syndrome* Q | Coarctation Of Aorta Q |
| | Pulmonic Q Stenosis (*in Noonan Syndrome*) |
| | Aortic Stenosis |
| *Holt Oram Syndrome* Q | Familial ASD Q (ASD with Bony Abnormalities) |
| *Marfan's Syndrome* Q | Aortic or Pulmonary Artery Dilatation |
| | Mitral Q or Aortic Regurgitation Q |
| *Ellis Van Crevald Syndrome* Q | ASD Q + Single Atrium |
| *Rubella* Q | PDA Q ( Most Common ), |
| | Pulmonary Stenosis Q |
| | *VSD* Q (according to CPDT/ Ghai) |

**Remember :**

- The strongest familial (genetic) tendency is known in 'Holt Oram Syndrome' Q
- The strongest environmental factor known is : High altitude Q
- There is higher incidence of patient ductus arteriosus and arterial septal defects in children born at high altitudes. (Memo : Increased oxygen tension is responsible for closure of ductus arteriosus.) Q

**413. Answer is C (Pulmonary stenosis):** *CPDT 15th/ 933, Nelson 17th/ 1925*

*Pulmonary stenosis is the most common cardiac abnormality in Noonan's syndrome.*

| Turner's syndrome | Noonan's syndrome |
|---|---|
| Most common cardiac defect associated is | *Most common cardiac defect associated is* |
| • Coarctation of aorta | • *Pulmonary valvular stenosis (most common)* |
| • Bicuspid aortic valve | • *Hypertrophic cardiomyopathy* |
| | • *ASD* |

**414. Answer is C (PDA):** Harrison 18th/p 1924 *Harrison 17th/1461; Ghai 6th/; Chandrasoma Taylor 3rd/ 342; Read text below*

*Differential cyanosis is a characteristic feature of Patent ductus arteriosus*

**415. Answer is D (Supravalvular Aortic stenosis):** *'The Art and Science of Cardiac Physical Examination' by Ranganathan and Vohe 1st/53*

*In supravalvular aortic stenosis the direction of jet of flow tends to be directly directed into the innominate artery. This often results in the direct impact pressure of the central jet being transmitted to right arm, thus making the right arm pressure higher than the left - 'The Art and Science of Cardiac Physical Examination' by Ranganathan and Vohe 1st/53.*

**416. Answer is C and E (Ebstein's anomaly and Single ventricle with pulmonic stenosis) :** *Harrisons 16th/1384*

*Ebstein's anomaly and single ventricle with pulmonic stenosis are associated with normal or decreased pulmonary blood flow*

*Truncus Arteriosus, complete TGA and TAPVC are associated with increased pulmonary blood flow.*

**Cyanotic Congenital Heart Disease**

| Increased pulmonary blood flow | Normal or decreased pulmonary blood flow |
|---|---|
| 1. ***Complete transposition of the great arteries*** | 1. *Tricuspid atresia* |
| 2. *Double- outlet right ventricle of the Taussing- Bing type* | 2. ***Ebstein's anomaly with right- to-let arterial shunt*** |
| 3. ***Truncus arteriosus*** | 3. *Pulmonary atresia with intact ventricular septum* |
| 4. ***Total anomalous pulmonary venous connection*** | 4. *Pulmonic stenosis or atresia with ventricular septal defect (tetralogy of Fallot)* |

| | |
|---|---|
| 5. *Single ventricle without pulmonic stenosis* | 5. *Pulmonic stenosis with Right – to – Left arterial shunt* |
| 6. *Common atrium* | 6. *Complete transposition of the great arteries with pulmonic stenosis* |
| 7. *Tetralogy of Fallot with pulmonary atresia and increased collateral arterial flow* | 7. *Double – Outlet right ventricle with pulmonic stenosis* |
| 8. *Tricuspid atresia with large ventricular septal defect and no pulmonic stenosis* | **8. *Single Ventricle with pulmonic Stenosis*** |
| 9. *Hypoplastic left heart (aortic atresia, itral atresia)* | 9. *Pulmonary arteriovenous fistula* |
| | 10. *Vena Caval to left arterial communication* |

**417. Answer is B (PDA) :** *Harrisons 16th/1384*

*Patent Ductus Arteriosus is not classified as a cyanotic congenital heart disease.*

*PDA is an Acyanotic Heart disease with Left to Right shunt*

**418. Answer is C (TOF):** *Ghai 6th/406 – 409; Harrisons 16th/399*

*ASD, LVF and VSD are all associated with pulmonary congestion and hence predispose to pulmonary infections. TOF is associated with reduced pulmonary blood flow (oligenic lung fields) due to right ventricular outflow obstruction and hence does not predispose to recurrent pulmonary infections.*

## Tetralogy of Fallot

**419. Answer is C (ASD):** *Ghai 6th/406*

*ASD is not part of the four constituents that characterize the tetralogy of fallot*

- **Tetralogy of Fallot:** *Ghai 6th*

Essential Criteria for Tetralogy of Fallot

- *Ventricular septal Defect*[Q]
- Right ventricular out flow tract obstruction (RV OT obstruction)
  *The most common cause of RVOT obstruction is infundibular stenosis*
  *Pulmonary valvular stenosis is less common and may or may not be present*
- *Right ventricular Hypertrophy*[Q]
- Dilated (Overriding) Aorta

- **Pentalogy of Fallot** *(Dorland's 28th/1253; Stedman's 28th/1452)*

Association of four defects occurring in Tetralogy of Fallot with either ASD or Patent Foramen Ovale.

| Pantalogy of Fallot | = | Tetralogy of Fallot | + | Atrial Septal Defect (ASD) OR Patent Foramen Ovale |
|---|---|---|---|---|

- **Trilogy of Fallot:** *Dorland's 28th/1746; Stedman's 28th/2033*

Applied to the combination of Pulmonic Stenosis, ASD and Right Ventricular Hypertrophy

**Trilogy of Fallot**

- *Pulmonic Stenosis*
- *Atrial Septal Defect (ASD)*
- *Right Ventricular Hypertrophy*

**420. Answer is A (Valvular Stenosis):** *CMDT 2007 / 328*

*Valvular stenosis is not an essential criteria for Tetralogy of Fallot according to CMDT*

*'Patients with Tetralogy of Fallot have a VSD, RV infundibular stenosis, RV hypertrophy and dilated (overriding) aorta. There may or may not be pulmonary valve stenosis (valvular stenosis) as well' - CMDT*

**421. Answer is A (ASD):** *Dorland's Medical Dictionary 28th/1253, 1746; Stedman's Medical Dictionary 28th/1452*

***Pentalogy of Fallot encompasses the four defects included in Tetralogy of Fallot together with patent foramen ovale or atrial septal defect.***

| Pantalogy of Fallot | = | Tetralogy of Fallot | + | Atrial Septal Defect (ASD) OR Patent Foramen Ovale |
|---|---|---|---|---|

**422. Answer is D (First Heart Sound is soft) :** *Ghai 6th/408*

***First heart sound (S1) is normal in Tetralogy of Fallot.***

Physical Examination in Tetralogy of fallot

**General Examination**

- *Cyanosis present*
- *Clubbing present*
- *Normal Arterial pulse*
- *Normal JVP (a wave may be slightly prominent)*

**Auscultation**

**Heart Sounds**

- *S1 : Normal*
- *S2 : Single*

*Only $A_2$ Heard*
*$P_2$ is soft, delayed and inaudible*

**Heart murmur**

**Shunt murmur** (VSD) Absent
**Flow Murmur** : *Pulmonory ejection systolic murmur located in left third intercostal space present*

*The murmur in tetralogy of Fallot relates to the degree of right ventricular outflow obstruction (pulmonic stenosis). It is a harsh ejection systolic murmur resulting from turbulent flow across the stenotic pulmonic valve*
*The shunt murmur is absent because the shunt operates at a low pressure difference*

**423. Answer is C (Predominantly left to right shunt):** *Ghai 6th/406-409*

***Tetralogy of fallot is associated with a predominant Right to left shunt***

**Tetralogy of fallot is associated with a predominant Right to left shunt**

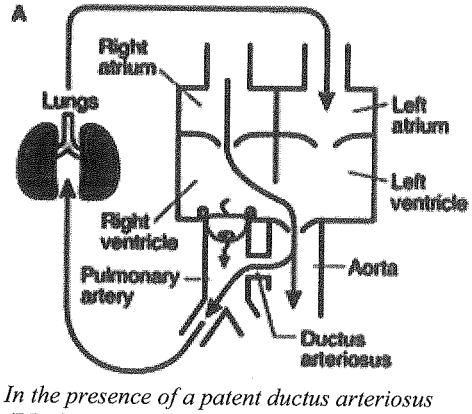
*Tetralogy of fallot is associated with Right ventricular out flow tract obstruction due to Pulmonic Stenosis*
*This results in flow of blood from right to left across the VSD into the aorta – **Predominant Right to left shunt***

**When the ductus arteriosus in patent i.e In the presence of patent Ductus Arteriosus**

↓

Unoxygenated blood can flow through the PDA into the lungs and become oxygenated

A



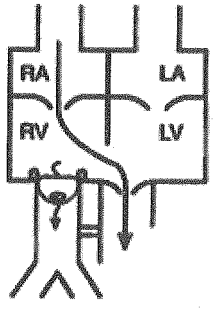

*In the presence of a patent ductus arteriosus (PDA), unoxygenated blood can flow through the PDA to the lungs and become oxygenated.*

**When the ductus arteriosus closes after birth In the absence of patent ductus Arteriosus**

↓

Unoxygenated blood is transmitted to the systemic circulation and the infant becomes cyanotic

B




*When the ductus arteriosus closes after birth, unoxygenated blood is transmitted to the systemic circulation and the infant becomes cyanotic*

*Diagram shows the four cardiac chambers, the stenotic pulmonic valve, the perimembranous ventricular septal defect, and the overriding aorta.*

**424. Answer is D (Tetralogy of Fallot) :** *Ghai 5th /303*

*'Coeur en Sabot' refers to the radialogical appearance of heart in a patient with Tetralogy of Fallot.*
The cardiac silhouette resembles that of a'boot' or *Wooden shoe in 'Coeur en Sabot' [boot shaped heart*[Q]*].*

**425. Answer is A (Aorta to Pulmonary Artery):** *Ghai 6th/409 Nelson 17th*

*Blalock Taussig shunt consists of subclavian artery (br. of aorta) and pulmonary artery anastamosis. This inturn actually establishes a shunt between the aorta (Via the subclavian artery) and the pulmonary artery.*
The concept is to anastamose a systemic artery to the pulmonary artery to increase the blood flowing through the lungs and thus increase the amount of oxygenated blood reaching the systemic circulation. Amongst the options provided the single best answer is the anastomosis between aorta and pulmonary artery.

Surgical management of Tetralogy of fallot

| Palliative | Definitive |
|---|---|
| Anastamosing a systemic artery with the pulmonary artery to increase the pulmonary blood flow and thus increase the amount of oxygenated blood reaching the systemic circulation | Consist in closing the ventriculer septal defect and resecting the infundibular obstruction. |

| Shunt | | Anastomosis |
|---|---|---|
| Blalock-Taussig shunt | : | Subclavian artery- Pulmonary artery |
| Pott's shunt | : | Descending aorta- Pulmonary artery |
| Waterson shunt | : | Ascending aorta- Palmonary artery |

**426. Answer is B (Descending aorta with left pulmonary artery) :** *Sabiston 15th/2023-4*

*Pott's shunt involves anastomosis between descending aorta and pulmonary artery*

*Palliative treatment in Fallot's Tetralogy consists of anastamosing a systemic artery with the pulmonary artery to increase the pulmonary blood flow and thus increase the amount of oxygenated blood reaching the systemic circulation. These palliative procedures prolong life and increase exercise tolerance.*

There are three such systemic - pulmonary anastamosis:

1. *Ballock Tausigg shunt*[Q] : Anastamosis between subclavian artery and pulmonary artery. [Q]
2. **Potts shunt**[Q] **:** Anastamosis between descending aorta and pulmonary artery.[Q]
3. Waterson shunt : Anastamosis between ascending aorta and right pulmonary artery.

**427. Answer is C and D (VSD and Blalock taussig shunt ...):** *Ghai 6th/406-409*

*Ventricular septal Defect is a constituent of Tetralogy of Fallot*
*Blalock Taussig shunt consists of subclavian artery – Pulmonary artery anastomosis*

*Tetralogy of Fallot is associated wit Right axis deviation*
*Tetralogy of Fallot is associated with right ventricular Hypertrophy*
*Morphine is indicated in the management of Anoxic Spells*

## Atrial Septal Defect

**428. Answer is C (Ostium primum atrial septal defect):** Harrison 18th/p 1921, 1922 *Harrison 17th/1459, 1460; O.P. Ghai 6th/ 401*

*Wide fixed splitting of $S_2$ with ejection systolic murmur in left 2nd intercostal space points towards the diagnosis of Atrial septal defect.. Presence of left axis deviation indicates an ostium primum ASD.*

**Clinical picture in ASD :** *Ghai 6th/ 401*

| Sounds | Murmur | ECG |
|---|---|---|
| • $S_1$ *Accentuated (Loud)* Q<br>• *S2 wide* fixed split Q | • *Shunt murmur : is absent i.e. there is no murmur as a result of shunt*<br>• *Flow murmurs:* murmurs present are due to increased flow of blood through respective valves<br>Tricuspid valve: Delayed diastolic<br>Pulmonary valve Ejection systolic | Ostium primum Q: Left axis deviation<br>Ostium secundum Q: Right axis deviation + RVH |

**429. Answer is B (Left aterial hypertrophy):** Harrison 18th/p 1921, 1922 *Harrison 17th/1459, 1460; Ghai 5th/ 296, Ghai 6th/ 400, 401; Read text below*

*ASD is associated with RA and RV hypertrophy but not LA hypertrophy.*

Left Atrium has two outflow tracts in ASD
- into L.V. through mitral valve
- into R.A. through ASD

- With two outflow tracts the resistance against which the L.A. has to pump is decreased
  - *this explains absence of L.A. hypertrophy*
- Right atrial load, however is increased and so is the load to R.V. and Pulmonary vessels
  - *this explains R.A. and R.V. hypertrophy as well as pulmonary hypertension*

**Remember :**

- Most common form of ASD is : Ostium secundum Q
- Lutembacher syndrome is : ASD + Mitral stenosis Q
- Patients with ASD are generally asymptomatic Q
- Congestive cardiac failure is rare in patients with ASD (it almost never occurs in patients with T.O.F.) Q
- Infective endocarditis is very rare in patients with ASD (because pressure gradient is very less) Q
- In ASD pulmonary flow is greater than systemic flow (Hilar dance and pulmonary plethora are seen) Q
- High incidence of ASD is seen in patients with Down's syndrome. Q

**430. Answer is B (Left parasternal heeve is due to increased pulmonary artery flow) :** *Ghai 5th/296*

*In ASD large volume of blood reaches the left atrium, right atrium, right ventricle and Pulmonary circulation.*

*Consequently* ***there is enlargement of LA, RV as well as of the pulmonary artery and its branches, and this may contribute to the left parasternal haeve.***

***ASD is a defect in atrial septum and not in patent foramen ovale.*** Q

***$S_2$ is wide and fixed (not variable). P2 is accentuated.*** Q

***Systolic murmur in ASD is not caused by rapid flow of blood across the shunt.***
*There is only a minor difference of pressure between the left and the right atrium. The shunt murmurs is therefore absent.* Q

*Murmurs present are flow murmurs and not shunt murmurs* :
- Delayed diastolic murmurs : due to increased flow across the tricuspid valve
- Ejection systolic : due to increased flow across the pulmonary valve

**431. Answer is C (Ostium primum with floppy mitral valve):** *'Pediatrics: A concise Text' by Kabra & Srivastava (Elsevier, India) 2010/135, Instant Pediatrics' by Agarwal (Ane Books)2008/86*

***'Presence of a pansystolic murmur of mitral regurgitation with left axis deviation in a patient with ASD suggests the presence of ostium primum defect with a cleft mitral valve leaflet or a floppy mitral valve with mitral valve prolapse'***
*- Pediatrics: A concise Text (Elsevier)2010/135*

| Presence of Pansystolic Murmur in a patient with ASD suggests. |
|---|
| • *Ostium Primum Defect* |
| • *Floppy mitral valve* |
| • *Cleft mitral valve* |
| • *Associated Rheumatic Mitral Regurgitation* |

| ASD type | ECG |
|---|---|
| *Ostium Primum* | *Left Axis Deviation* |
| *Ostium Secondum* | *Right Axis Deviation* |

**432. Answer is B (ASD):** *Ghai 6th/400*

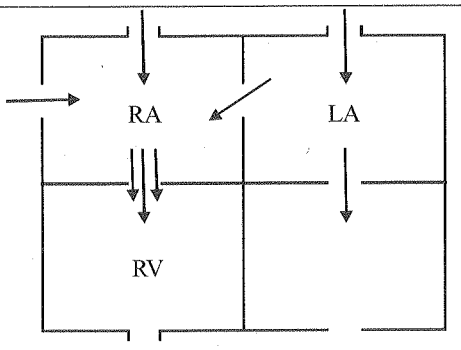
*ASD is associated with an enlarged right atrium & right ventricle to accommodate large volume of blood. The left atrium is not enlarged because it decompresses itself by shunting blood to the right atrium at a minor difference in pressure.* ***The left atrium may enlarge once Eisen menger's syndrome develops and a reversal of shunt is seen across the defect.***

**Right Atrium :**

***'Enlarges to accommodate the extravolume of blood'*** *– Ghai*
- Shunted blood from LA
- blood from IVC
- blood from SVC

**Right Ventricle :**

***Enlarges to accommodate the large volume of blood reaching from the left atrium*** *- Ghai*




**Left Atrium :**

- Empties into the RA and the LV and does not accommodate any extra blood and hence is ***not enlarged***

**Left ventricle :**

- Receives *less blood from LA than normal as some blood is shunted to RA & RV and hence is* ***not enlarged.***

## Ventricular Septal Defect (VSD)

**433. Answer is D (Pulmonary oligemia in X ray chest):** *Ghai 5th/ 298, 299, Ghai 6th/ 402, 403*

*V.S.D. is characterized by pulmonary plethora and not pulmonary oligemia.*
***Pulmonary vasculature is increased*** *– Ghai 6th/403*

- **Chest X-ray in VSD does not show pulmonary oligemia.**
  A ventricular septal defect results in shunting of oxygenated blood from left ventricle to the right ventricle. This left to right shunt therefore streams the blood to the pulmonary artery and then to the lungs. *The pulmonary vasculature is thus increased and pulmonary plethora is seen.*
- **Small holes in VSD may close spontaneously**
  Disappearance of ventricular defects is called spontaneous closure. *Almost 70-80 percent of all ventricular defects become smaller in size or disappear entirely*
- **Defect in VSD is usually in membranous part.**
  *90% defects are located in the membranous part – Ghai 6th/402*
- **Endocarditis is commonest complication of VSD.**
  VSD is the *commonest congenital lesion complicated by infective endocarditis – Ghai 6th/404.*

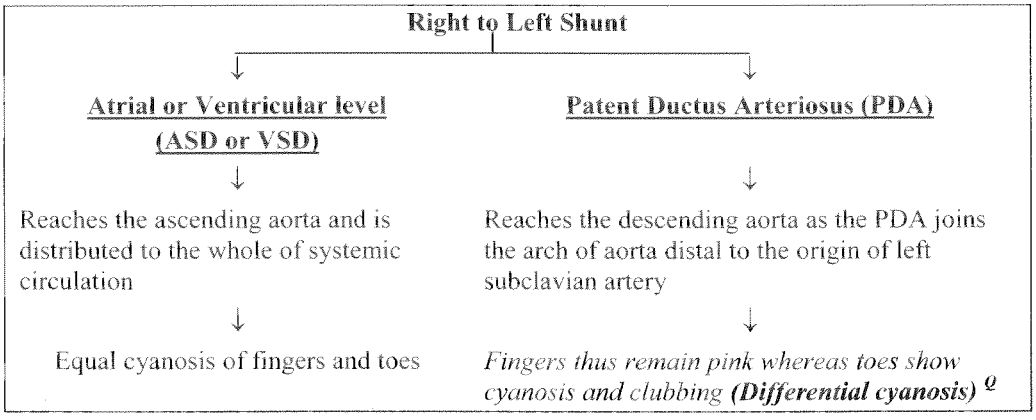
## Patent Ductus Arteriosus (PDA)

**434. Answer is C (PDA):** *Harrison 18th/1924; 17th/1461; Ghai 6th/; Chandrasoma Taylor 3rd/ 342; Read text below*

*Differential cyanosis is a characteristic feature of Patent ductus arteriosus*

**Cyanosis** is bluish discoloration of skin and mucus membranes caused by increased amount of reduced hemoglobin in arterial blood.

In congenital heart disease, cyanosis is caused by right to left shunt, which allows unoxygenated venous blood to bypass the lungs and enter systemic circulation.




**435. Answer is D (May cause machinery murmur by its patency) :** *Langman Embryology 6th/223*

*Shunt murmur in patent ductus arteriosus is a continuous machinery murmur.*

- **Anatomic closure of Ductus arteriosus may take upto three months.**
  Physiological closure (mediated by bradykinin) occurs almost immediately after birth by contraction of its muscular wall.

  ***Anatomic closure occurs by proliferation of intima, and may take from 1-3 months*** Q ***(& not in 24 hrs).***

- **Ductus arteriosus after obliteration forms ligamentum arteriosum.** Q **(& not the ligamentum venosum)**
  - *Closure of the ductus venosus forms the Ligamentum venosum.*
  - *Closure of distal part of umbilical arteries → forms medial umbilical ligament.* Q
  - *The proximal part of umbilical artery remains patent as the "superior vesical artery".* Q
  - *Closure of umbilical vein → forms the ligamentum teres hepatis.* Q

- **Prostaglandins maintain patency of ductus arteriosus, and do not induce it to close**
  *"In neonates with congenital heart defects, till surgery is undertaken, $PGE_1$ (Alprostadil) is used to maintain patency of ductus arteriosus".- KDT4th/219*
  *Prostaglandins maintains patency of ductus arteriosus*
  *NSAIDs - help in early closure of ducts arteriosus*

- **Ductus arteriosus may cause a machinary murmur by its patency.**
  *"Shunt murmur is a continuous machinery murmur". - Ghai 5th/301*
  The murmur is best heard at the 2nd left intercostal space and is also well heard below the left clavicle, where it maintains its continuous machinery character.

**436. Answer is A and B (CCF and Infective Endocarditis) :** *Harrisons 16th/1386*

*The leading causes of death in adults with patient ductus are cardiac failure and infective endocarditis.*
*-Harrisons 16th /1386*

## Tricuspid Atresia

**437. Answer is D (Splliting of $S_2$):** *Ghai 6th/408, 410, 414-415; Nelson 17th/1531*

*Tricuspid Atresia is associated with a single S2 and not a split S2*

**Tricuspid Atresia is associated with Right Ventricular hypoplasia.**
**Atresia of the tricuspid valve** results in the absence of a communication between the right atrium and right ventricle therefore the **right ventricle is underdeveloped the inflow portion being absent**.
**Tricuspid Atresia is associated with Left ventricular hypertrophy and Left Axis Deviation**
The only exit for systemic venous blood coming to the right atrium is by way of *Atrial Septal defect*. Through this the blood goes to left atrium from where it enters left ventricle.

A *ventricular septal defect* provides communication between the left ventricle and the outflow portion of the right ventricle. The *left ventricle therefore maintain both the systemic as well as the pulmonary circulation* thus there is **hypertrophy of the left ventricle** which is reflected by ***left axis deviation in ECG****.

**Pulmonary vascularity is diminished**
***90% patients of Triscuspid Atresia have diminished blood flow.***

**Single S2 is seen in Tricuspid Atresia**
*Tricuspid Atresia is associated with a Normal S1 and single S2.*

**438. Answer is A i.e. Tricuspid atresia:** *Ghai 6th/408-415; Nelson 17th/1531*

*Tricuspid atresia causes left ventricular hypertrophy and left axis deviation.*
*All other options cause right ventricular hypertrophy and right axis deviation.*

*"Left axis deviation and left ventricular hypertrophy are usually present on electrocardiogram distinguishing tricuspid atresia from most other cyanotic heart lesions.*
*The combination of cyanosis and left axis deviation is highly suggestive of tricuspid atresia." - Nelson 16th/1391*

**439. Answer is B (Tricuspid Atresia):** *Ghai 5th/304*

*Presence of Left Ventricular hypertrophy and left axis deviation on ECG in a child suggests a diagnosis of Trocuspid atresia.*

**Tricuspid Atresia**

Congenital absence of tricuspid valve is called tricuspid atresia.

**Haemodynamics:**
- *The inflow portion of R.V. is hypoplastic* Q
- *The systemic venous blood coming to R.A. exits by way of a patent foramen ovale or an ASD.* Q
- *A VSD provides communication between L.V. and outflow portion of R.V.* Q
  *The L.V. thus maintains both the systemic and pulmonary circulation.* Q
- *The saturation of blood in the pulmonary artery and aorta is identical.* Q
- *The pulmonary blood flow is dependent on size of VSD* Q
- *The VSD in tricuspid atresia is always a muscular defect.* Q

**Features suggestive of tricuspid atresia :**
- ***L.V. type of apical impulse*** Q
- *Prominent large 'a' waves* Q
- *Enlarged liver with presystolic pulsations (a waves)* Q
- ***ECG characterised by Left axis deviation and Left ventricular hypertrophy.*** Q

**Clinical features :** (are similar to Fallot's tetralogy Q)
- *Child is cyanotic from birth* Q
- *Anoxic spells and squatting may be present* Q

**440. Answer is B (Tricuspid Atresia):** *Ghai 6th/410*

*Tricuspid Atresia is associated with Left Axis deviation and not Right Axis deviation.*
Symptoms and signs of Tricuspid Atresia are similar to those of Tetralogy of Fallot.

Features suggesting Tricuspid Atresia are
- Left ventricular type of apical impulse
- Prominent large 'a' waves in JVP
- Enlarged liver and presystolic pulsations (a waves)
- Left axis deviation and left ventricular hypertrophy on ECG

**441. Answer is B (Downward displacement of an abnormal tricuspid valve into right ventricle):** *Ghai 7th/411*

***Ebstein's anomaly is characterized by downward displacement of an abnormal tricuspid valve (Septal and posterior leaflet) into the right ventricle such that the portion of the right ventricle above the displaced tricuspid valve leaflets becomes part of the right atrium (Atrialized Right Ventricle).***

**Ebstein's Anomaly**

- *The normal Tricuspid Valve has three leaflets (Anterior; Posterior; Septal).*
- *Ebstein's anomaly is characterized by Downward (Apical) displacement of the Septal and Posterior leaflets into the Right Ventricle*

The principle feature of Ebstein's anomaly is apical displacement of the septal leaflet of the tricuspid valve from the insertion of the anterior leaflet of the mitral valve by at least 8 mm/m$^2$ body surface area.

- *The anterior leaflet which is formed at a different stage of development usually retains a normal position though it may be redundant, fenestrated or tethered*
- *Overall the functional annulus is displaced downward (Apical) into the right ventricle.*
- *The portion of the right ventricle above the displaced annulus becomes Atrialized (Atrialized Right Ventricle).*
- *The right atrium and atrialized right ventricle becomes dilated with variable degrees of hypertrophy and thinning of the wall.*
- *The true tricuspid annulus is also dilated.*

## Coarctation of Aorta

**442. Answer is D (Coarctation of aorta):** Harrison 18th/p 1925 *Harrison 14th/ 306, Harrison 15th/ 1337, Harrison 16th/ 1387; Harrison 17th/1462*

*Intermittent claudication, dizziness and headache are all suggestive of coarctation of aorta*

**Coarctation of Aorta: Review**

**Clinical presentation :**

- Most patients are asymptomatic Q
- Symptomatic patients usually present with :
  - *Headache, dizziness,* Q
  - Epistaxis
  - *Cold extremities, and weakness in the legs* Q
  - ***Claudication with exercise*** Q
- Hypertension in upper extremities with marked diminution of pulsation in lower extremities. Q
- Mid systolic or continuous murmur over anterior part of chest and back Q
- Enlarged and pulsatile collateral vessels in intercostal spaces anteriorly in axilla or posteriorly in interscapular area Q
- Upper extremity and thorax may be more developed than lower extremities. Q

**Investigations :**

- ECG: shows L.V. Hypertrophy Q
- Radiography :
  - *Indentation of aorta at site of coarctation and '3 sign' on paramediastinal shaddon are almost pathogenic.* Q
  - *Notching* (erosion) of inferior surfaces of ribs. Q

**Complications :**

- Cerebral aneurysms and haemorrhage Q
- Rupture of aorta
- Left ventricular failure Q
- Infective endocarditis Q

**Treatment :**

- Is surgical *resection* Q of 'coarctation' and end to end anastomosis
  *Remember that HT may not be corrected even after surgical correction of the 'coarctation'.* Q

Few other questions :

| | | |
|---|---|---|
| *Most common site* Q of coarctation of aorta | : | *distal to origin of left subclavian artery.* Q |
| *Most common associated cardiac anomaly* Q | : | *bicuspid aortic valve.* Q |
| *May be associated with* Q | : | *Turner's syndrome.* Q |

**443. Answer is B (Coarctation of aorta):** *Ghai 6th/419*

*Feeble femoral pulsations compared to strong brachial pulsations suggests the diagnosis of coarctation of aorta.*

*Hypertension and strong pulsations in the upper extremities and absence, marked dimunition or delay in pulsations in the femoral artery are characteristic in coarctation. Also failure to thrive and congestive heart failure are consistent with the diagnosis of congestive heart failure.*

**Coarctation of Aorta:** *Ghai*

- *'Physical examination shows delayed and weak or impalpable femorals compared to strong brochial arteries'-Ghai*
- *'Coarctation may result in congestive heart failure in infancy'-Ghai*
  *(in congestive failure does not occur in infancy it is unlikely to occur throughout the pediatric age group unless complicated by infective endocarditis or anemia)*
- *Failure to thrive is a manifestation of congestive heart failure.*

**Remember:**

- *Differential cyanosis is a manifestation of PDA*[Q]
- *Differential pulses/Blood pressure is a manifestation of Coarctation*[Q]

**444. Answer is D (Boot Shaped Heart):** *Chest Radiographic Interpretation in Pediatric Cardiac Patients (Thieme) 2011/ 81*

***Boot Shaped Heart is not a radiological feature of Coarctation of Aorta.*** *Boot Shaped Heart is typically seen in Tetralogy of Fallot.*

| **Boot Shaped Heart (Couer en Sabot)** |
|---|
| ***Tetralogy of Fallot and Tetralogy of Fallot with pulmonary atresia (Pulmonary atresia with VSD)*** |

*Note that a Boot Shaped Heart may also be seen in Truncus Arteriosus (less commonly)*

***Coarctation of Aorta*** *is associated with Hypertension in upper extremity with* ***marked diminution of pulsation in lower extremities****. Coarctation is also typically associated with* ***Left Ventricular Hypertrophy*** *from pressure overload.* ***Bicuspid Aortic Valve*** *is the most common associated cardiac anomaly in patients with Coarctation. Typical Radiological signs in Coarctation include Indentation of Aorta at site of Coarctation and '3 Sign' or para-mediastinal shadow together with notching of inferior surface of ribs.*

**445. Answer is C (Coarctation of aorta):** *Harrison 18th/1925 Harrison 16th/e 1387; Harrison 17th/1462; Previous questions*

*Hypertension in upper extremity with absence, dimunition or delay in pulsations in lower extremity suggests the diagnosis of coarctation of aorta. Other options have been explained in the previous questions.*

***Murmurs in coarctation of aorta:***

| **Murmur due to the narrowing or coarctation** | **Flow murmur across collaterals** |
|---|---|
| Midsystolic or continuous mumur over the anterior part of chest, back and spinous processes due to narrowing of lumen and resultant high velocity jet | Systolic or continuous mumur over lateral thoracic wall due to increased flow through dilated and tortuous collateral vessels. |

**446. Answer is B (Coarctation of aorta):** *Harrison 18th/1925; 15th/ 1337; Harrison 16th/1387; Harrison 17th/1462*

*Hypertension in the upper extremities and absence, marked diminution or delayed pulsations in the femoral arteries are on physical examination are characteristic in coarctation of aorta – Harrison 16th/ 1387*
***Associated notching of ribs along the lower border leaves no doubt as regards the correct diagnosis.***

**447. Answer is D (Coarctation of Aorta):** *SOAP for Cardiology (2006) /100, 101; Moss and Adam's 7th/1288; Nelson's 18th/1900, 1901; Hurst 11th/ed 1809; Oski's Pediatrics 2nd/714; 'Pediatrics' Board Review Series 2nd/341*

***Isolated upper extremity hypertension (200 / 140 mm Hg), together with absent/ diminished femoral pulses is a characteristic feature of coarctation of aorta.***
*Although coarctation of aorta does not commonly present with seizures, these may be seen as a consequence of severe hypertension (BP = 200/140) or complications like intracranial haemorrhage (from Berry aneurysms which are more common in patients with coarctation.*

**Coarctation of Aorta is the most likely diagnosis: Approach** *(Nelson/Hurst)*

- The classic sign of coarctation of aorta is a disparity in pulsations and blood pressure in arms and legs. *The femoral, popliteal, posterior tibial and dorsalis pedis pulses are weak (or absent in upto 40% of patients) in contrast to bounding pulses in the arms and carotid vessels.*
- The blood pressure is the legs is lower than in the arms and *90% of patients with coarctation have hypertension in an upper extremity* greater than 95$^{th}$ perecentile for age

| Age (yrs) | 95$^{th}$ percentile (mm Hg) |
|---|---|
| *> 1 yrs* | *110 / 60* |
| *1 – 5 yrs* | *115 /75* |
| *6 – 10 yrs* | *125 /85* |
| *11 – 18 yrs* | *140 /90* |

- *Severe hypertension* may be seen as a consequence of persistant hypertension in an individual who has not undergone corrective surgery for coarctation, and this usually *appears in the second or third decade of life (Hurst)*

> *A blood pressure of 200 /140 mm Hg in a 10 year old boy suggests severe hypertension (95$^{th}$ percentile at 10 years – 125/85)*

- ***Children with severe / malignant hypertension may develop headaches, seizures and stroke (haemorrhage from Berry aneurysms which are more common in patients with coarctation).***

**Takayasu Aortoarteritis may also present with severe hypertension and absent femoral pulses due to acquired midaortic coarctation but this is an uncommon presentation in Takayasu aortoarteritis (and hence not the single best answer of choice)**

Takayasu arteritis (or non specific aortoarteritis) is a chronic vasculitis disease of medium and large sized arteries with a strong predilection for aortic arch and its branches.
*This may lead to stenosis of the involved vessels and hence a picture of acquired coarctation.* It may thus produce a clinical picture similar to that of coarctation with disparity in pulsations and blood pressure in arms & legs with hypertension depending on the site of the acquired stenosis.

> However, this condition is *more common in women* and most *commonly affects the subclavican artery*. Hence it ***more commonly presents with*** claudication, along with unequal and ***reduced pulses / BP in the upper extremity*** than the lower extremity. Also *systemic symptoms are more common* is Takayasu than in coarctation. *Nevertheless Takayasu arteritis may affect the Thoracic or Abdominal aorta and present with absent lower limb pulses and upper extremity hypertension like coarctation of aorta.*
> *Takayasu arteritis can be picked as the answer if Coarctation of aorta is not provided amongst the options*

| Coarctation | Takayasu |
|---|---|
| • More common condition | • Less common condition |
| • More common in boys | • More common in girls (8 : 1 = F:M) |
| • Upper extremity hypertension | • Absent or decreased upper limb pulses (brachial / radial) and blood pressure difference between left and right arm is characteristic *('Reverse coarctation': Oski's Essential Pediatrics)* |
| • Bounding pulses in with arms and diminished / absent lower limb pulsations is characteristic | **Note** *Clinical picture similar to coarctation with absent lower limb pulsations and upper extremity hypertension may be seen if site of lesion is in the thoracic aorta / abdominal aorta (But this is not charachteristic).* |
| • Hypertension is frequent | • Hypertension is frequent |

**Renal Parenchymal Disease and Grandmal seizures do not present with isolated upper extremity hypertension and absent femoral pulses.**

**448. Answer is D (Coarctation of aorta):** *Harrison 14$^{th}$ /1306 (Repeat), 15$^{th}$/1337*

*The child is presenting with characteristic features of coarctation of aorta.*

**449. Answer is C (Coarctation of aorta):** Harrison 18th/p 1925, 1926 *Harrison 17th/1462; Refer text below*

*Classical clinical presentation with characteristic notching of ribs is diagnostic of coarctation of aorta.*

**Remember:**

- *Rib signs are unusual before 10 yrs of age*
- *Notching affects inferior surface of ribs*
- *Unilateral and right sided ribs are affected if the coarctation is proximal to the left subclavian artery*

**450. Answer is C (Inability to augment cardiac output with exercise):** *Harrison 15th/ 1337 Q 22 (CVS) pre test based on Harrison 15th/, Harrison 16th/ 1387; Harrison 17th/1462, 1463* Harrison 18th/p 1925

*In coarctation of aorta unless the hypertension is very severe or left ventricular failure has ensued, cardiac output responds normally to exercise.*

- *Usually a systolic ejection murmur is heard anteriorly and over the back. If the obstruction is very severe a continuous murmur would be heard. Coarctation of aorta is commonly accompanied by a bicuspid aortic valve, which can produce the diastolic murmur of aortic regurgitation.*
- Coarctation of the Aorta usually occurs just distal to the origin of the left subclavian artery. If it arises above the left subclavian, Arterial blood pressure elevation may be evident only in the right arm.
- In coarctation of aorta unless the hypertension is very severe or left ventricular failure has ensued, cardiac output responds normally to exercise.
- Hypertension is the major clinical problem and may persist even after complete surgical correction.

**451. Answer is A (Most common site is distal to the origin of left subclavian artery) :** *Harrison 14th/ 1306; Harrison 15th/1337; Nelson 15th / 1302*

*The most common site of coarctation of aorta is distal to the origin of left subclavian artery.*

*Notching occurs on Inferior surface* and not on the superior surface.
*L.V. Hypertrophy is prominent and not RV hypertrophy.*
It is the L.V. which is subjected to increased afterload because of the coarctation, and therefore L.V. Hypertrophy is the prominent finding. Q

*Most common age of presentation in coarctation of aorta is during infancy or early childhood*
*Only about 20 percent of patients with mild disease present during adolescence and adulthood*

**452. Answer is B (Bicuspid Aortic Valve):** Harrison 18th/p 1925 *Harrison's 17th /1462.*

*The most common associated cardiac anomaly with coarctation of aorta is bicuspid aortic valve* (Harrison's 17th /1462)
*Coarctation of aorta is associated with a bicuspid aortic valve in more than 70% of cases* - (Nelson 18th /1900)

**Associated anomalies with coarctation of Aorta** Q

- ***Bicuspid Aortic valve*** Q ***(commonest)***
- *PDA* Q
- *VSD* Q
- *Tubular hypoplasia of aortic arch* Q
- *Aortic stenosis* Q *(valvular / subvalvular)*

*Other Associated lesions that have been asked previously*

- *Mitral valve abnormalities*
  *(Subvalvular mitral ring /parachute mitral valve)*
- *Turner's syndrome* Q

**Shone complex** Q

Coarctation of Aorta
+
Left sided obstructive lesions
*(Mitral valve abnormalities and subaortic stenosis)*

**453. Answer is A (Bicuspid Aortic valve):** *Harrison 18th/p 1925 Harrison's 17th /1462.*

*The most common associated cardiac anomaly with coarctation of aorta is bicuspid aortic valve -Harrison's 17th /1462*
*Coarctation of aorta is associated with a bicuspid aortic valve in more than 70% of cases - (Nelson 18th /1900)*

**454. Answer is C (Pulmonary stenosis):** Harrison 18th/p 1925 *Harrison 17th/1462; CPDT 15th/ 498*

*Coarctation of aorta is not associated with Pulmonary stenosis.*

| Coarctation Syndrome |
|---|
| • Coarctation of aorta |
| • Patent ductus arteriosus |
| • Bicuspid aortic valve |
| • Tubular hypoplasia of aortic isthumus |
| • VSD |

*Coarctation of aorta is also seen in Turner's syndrome – Harrison*

| | |
|---|---|
| Turner's Syndrome | • Coarctation<br>• Bicuspid valve / stenosis |

**455. Answer is C (Renal artery stenosis):** *Harrison 18th/p 1925 Harrison 15th/ 1332; 16th / 1383; 17th/1462; Ghai 6th /419*

*Renal artery stenosis is not associated with any form of congenital heart disease. In young it is usually a result of fibromuscular dysplasia and in elderly due to atheromatous plaques secondary to hypertension and diabetes.*

- ***Turner's syndrome*** is associated with *coarctation of aorta* and *bicuspid valve*. - *Harrison 14th / 1302*
- *Most common associated congenital cardiac anomaly with coarctation of aorta* is bicuspid aortic valve-*Harrison 14th / 1306, 15th /1337*
- *PDA may be associated.*

**456. Answer is B (Turner's syndrome):** *Nelson 16th / 1747*

*Turner's syndrome is commonly associated with coarctation of aorta.*

| Congenital Syndromes | Cardiac anomaly |
|---|---|
| Turner's syndrome | ***Coarctation of Aorta*** $^{Q}$<br>*Pulmonic stenosis* $^{Q}$<br>*Aortic stenosis* $^{Q}$ |
| Down's syndrome | *ASD* $^{Q}$ - endocardial cushion type |
| Noonan's syndrome *(Nelson 6th / 1747)* | *Pulmonary stenosis* $^{Q}$<br>ASD<br>Hypertrophic cardiomyopathy |

**457. Answer is D (Neurofibromatosis) :** *Radiology by Wolfgang Dahnert 5th/ 19; Grainger & Allison's 5th / 551*

*Neurofibromatosis is associated with superior rib notching*

***Inferior rib notching is characteristically seen in coarctation of Aorta and may also be seen in Superior vena cava obstruction and a Blalock-Taussig shunt*** $^{Q}$ ***operation***

**Rib-Signs in Coarctation of aorta:**

- ***Inferior rib notching*** $^{Q}$ is characteristic, and is believed to be due to *pressure erosion by intercostal arteries.*
- ***Inferior rib notching*** $^{Q}$ takes several years to develop and is ***rarely seen before the age of 8 years.*** $^{Q}$
- ***'3' sign*** $^{Q}$ may be seen due to enlargement of *left subclavian artery* above the coarctation
- ***Usually spares fist two ribs*** $^{Q}$ where intercostal arteries arise from costocervical trunk which is proximal to the usual site of CA. *Mostly commonly affected ribs are the 4th to 8th ribs.*
- ***Usually bilateral but asymmetrical.***

| **Unilater left notching** (absent on right side) |
|---|
| • *Anomalous origin of right subclavian artery distal to coarctation* |

| **U/L right notching** (absent on left side) |
|---|
| • *Stenosed / occluded left subclavian artery* |
| • *Coarctation is proximal to left subclavian.* |

**Causes of Rib notching:**

| Superior R.N. | Inferior R.N. |
|---|---|
| Poliomyelitis | **Arterial** |
| Osteogenesis imperfecta | ***Coarctation of Aorta***[Q] |
| Restrictive lung disease | *Aortic thrombosis*[Q] |
| ***Neurofibromatosis***[Q] | ***Blalock-Taussig shunt***[Q] (Subclavian obstruction) |
| *Marfan's syndrome* | Pulmonary – oligemia / A-V malformation |
| Connective tissue disease | Pulmonary stenosis |
| - Rheumatoid Arthritis (RA) | Tetralogy of fallot |
| - *Systemic Lupus Erythematosis (SLE)* | Absent pulmonary artery |
| - Scleroderma | **Venous** |
| - Sjogren's syndrome | AV malformation of chest wall |
| - Hyperparathyroidism | ***Superior vena cava obstruction*** |
| | **Neurogenic** |
| | Intercostal neuroma |
| | Neurofibromatosis type 1 |
| | Poliomyelitis/quadriplegia/paraplegia |
| | **Osseous** |
| | Hyperparathyrpoidism |
| | Thalassemia |
| | Melnick-Needle Syndrome |

**458. Answer is C (Coarctation of Aorta):** *Radiology and imaging by Bhaduri/112*

***Rib notching and double bulge sign are characteristic radiological signs of coarcation of aorta.***

**Signs in coarctation of aorta**

| Abnormal Aortic arch | Inferior Rib notching |
|---|---|
| *Commonest finding*[Q]<br>*Site of narrowing may be seen as an identation.* [Q]<br>*Classic '3 sign'*[Q] or *double bulge sign'*[Q] on left border of aortic shadow is formed by (above downwards)<br>- prestenotic dilatation<br>- coarctation itself (indentation)<br>- poststenotic dilatation | *Is a frequent sign in adults. It is not seen until late childhood.*<br>***It is seen on the inferior margin of posterior halves of ribs from 3rd or 4th ribs downwards.***<br>Rib notching is *due to enlargement of intercostal arteries which act as collateral vessels.*<br>These collateral vessels produce indentation, on the ribs at the above sites. |

**459. Answer is D (Anterior MI):** *CMDT 2008/282, CSDT / 426*

***Myocardial Infarction has not been listed as a hazard /cause of death in coarctation of Aorta***

Causes of death in coarctation of Aorta (CSDT / CMDT)

- *Congestive Heart Failure*
- *Endo carditis*
- *Aortic Rupture*
- *Intracranial Hemorrhage* ┐ *Hypertension*
- *Aortic dissection* ┘

*Death is most frequently caused by complication of Hypertension such as stroke or aortic dissection. Other causes include endocarditis and congestive heart failure - Hurst 11th/1867*

## Total Anomalous Pulmonary Venous Connection (TAPVC)

**460. Answer is A (Supracardiac):** *Schwartz 8th/ 622*

***Type I** TAPVC with anomalous connection at the **supracardiac level** is the most common type accounting for about 45% of all cases.*

**Total anomalous pulmonary venous connection (TAPVC)** is characterized by abnormal drainage of pulmonary veins into the right heart either by direct connection into the right atrium or into its tributaries.

According to the site or level of connection of the pulmonary veins to the systemic venous system TAPVC has been classified into four types:

| | | |
|---|---|---|
| **Type 1 (45%)** | : | Anomalous connection at ***supracardiac level*** (Pulmonary veins drain into left innonimate vein or right SVC) |
| Type II (25%) | : | Anomalous connection at cardiac level (Pulmonary veins joint the coronary sinus or enter right atrium directly) |
| Type III (25%) | : | Anomalous connection at infracardiac level (Pulmonary veins drain into the portal vein) |
| Type IV (5%) | : | Anomalous connection at multiple levels |

**461. Answer is B (Always associated with VSD):** *Ghai 5th*

***TAPVC is not always associated with a VSD.***
*Communication between the left and the right heart, is either via ASD or a Patent Foramen Ovale.*

**TAPVC: is an uncommon congenital cyanotic heart disease.** Q

| Defect |
|---|
| All pulmonary veins are connected anomolously and reach the right Atrium directly or indirectly instead of reaching the left atrium. This may occur through the following ways (Anatomic classification): |
| *Anatomical Classification :* |
| Supracardiac : Pulmonary veins join together to form a common pulmonary vein which may drain either into the left brachiocephalic vein or Superior venacava to reach Rt Atrium.<br>Cardiac : The veins join the coronary sinus.<br>Infracardiac : The common pulmonary veins drain into portal vein.<br>*Remember : TheTAPVC of the infracardiac type is always obstructive, while cardiac and supracardiac types, may or may not have pulmonary venous obstruction.* Q |
| *Hemodynamics :* |
| The blood flow to the left atrium is the Rt to Left shunt via a patent foramen ovale or an ASD.<br>***Because mixing of blood occurs in Rt atrium, the oxygen saturation of blood in the pulmonary artery is identical or even higher to that in the aorta.*** Q |
| *Presentation :* |
| *Obstructive type:* presents with marked cyanosis and CHF within the first 1 - 2 weeks of life.<br>*Non obstructive type:* presents with cyanosis and CHF but presentation is delayed to around 4 to 10 weeks of age. |
| *X-ray chest* |
| *Snowman or figure of '8' configuration* Q<br>*Ground glass appearance :* (Characteristic of *Obstructive TAPVC.* Q) |

**462. Answer is B (Total Anomalous Pulmonary Venous Connection):** *Chest Radiographic Interpretation in Pediatric Cardiac Patients (Thieme) 2011/ 84*

***Snowman Shaped Heart or Figure of '8' Heart has typically been described in association with Total Anomalous Pulmonary Venous Connection (TAPVC).***

| ***Typical Shape*** | ***Classical Cause*** |
|---|---|
| *Boot Shaped Heart* | Tetralogy of Fallot |
| *Snowman Shaped Heart (Figure of 8 Heart)* | Total Anomalous Pulmonary Venous Connection to the Innominate Vein |
| *Egg on Side Appearance* | Complete Transposition of great arteries |
| *Figure of '3' Sign* | Coarctation of Aorta |

## Transposition of Great Vessels( TGV)

**463. Answer is B (Transposition of great vessels) :** *Read text below*

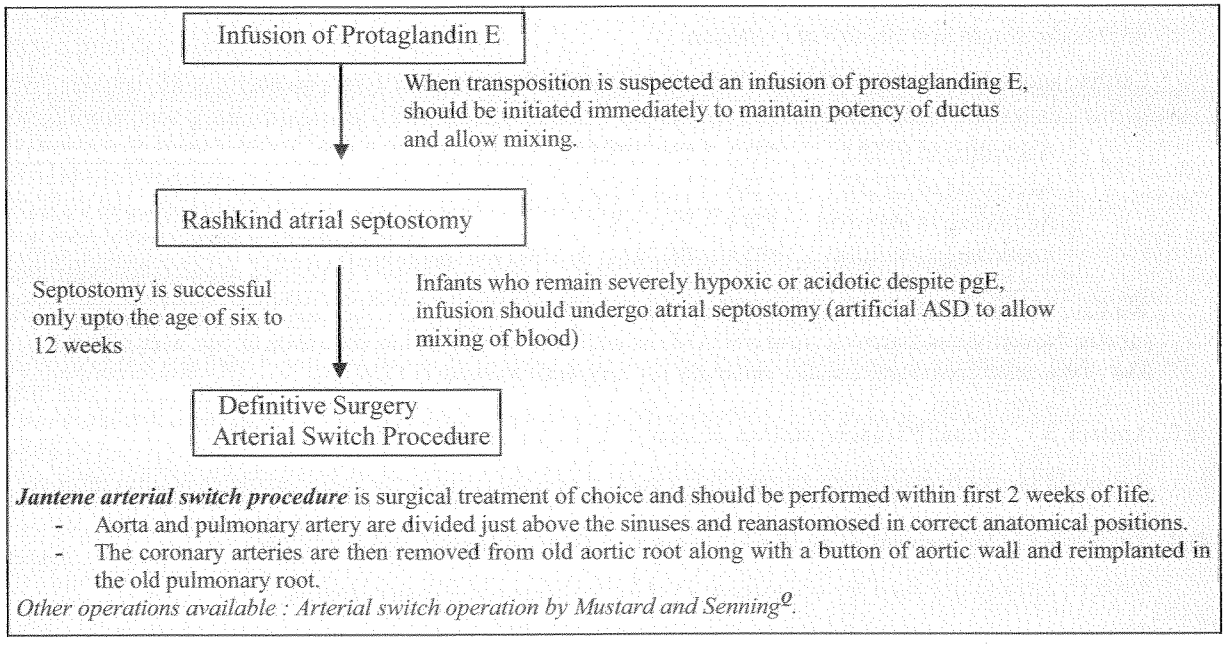
Transposition of Great vessels is a condition chracterized by aorta arising from the right ventricle and pulmonary artery from the left ventricle.

This results in complete separation of systemic and pulmonary circulation. Since systemic and pulmonary circulations are separate, survival depends on mixing of oxygenated pulmonary blood and deoxygenated *systemic blood which can occur:*

| | | |
|---|---|---|
| *At Atrial level* | : | *Through ASD* |
| *At Ventricle level* | : | *Through VSD* |
| *At Great vessel level* | : | *Through Patent ductus arteriosus* |

Oxygenation is normal in foetus but after birth as ductus arteriosus closes severe hypoxia occurs and in the absence of V.S.D, or ASD child presents with cyanosis and tachypnea at birth.

**Management of patients with transposition of great vessels**:




***Jantene arterial switch procedure*** is surgical treatment of choice and should be performed within first 2 weeks of life.

- Aorta and pulmonary artery are divided just above the sinuses and reanastomosed in correct anatomical positions.
- The coronary arteries are then removed from old aortic root along with a button of aortic wall and reimplanted in the old pulmonary root.

*Other operations available : Arterial switch operation by Mustard and Senning*[9].

## Anamolous Coronary Artery

**464. Answer is D (Anomalous coronary artery) :** *Nelson 15th/1308, Nelson 16th/1406*

***Characteristic symptoms of restlessness, irritability and diaphoresis on feeding and an increased risk of MI suggests a diagnosis of Anomalous Coronary artery.***

**Anomalous origin of the coronary arteries : anomalous origin of the left coronary artery from the pulmonary artery:**

In this anomaly the blood supply of the left ventricular myocardium is severely compromised. Soon after birth (Neonate) as the pulmonary arterial pressure falls, perfusion pressure to the left coronary artery becomes inadequate. ***Myocardial infarction and fibrosis may result.***

Clinical manifestion :

- Congestive heart failure becomes manifest within first few month of life and is often precipitated by respiratory infection.
- Recurrent attacks of discomfot, ***restlessness, irritability, diaphoresis***, dyspnea and pallor with or without cyanosis occur-could be caused by angina pectoris.
- Cardiac enlargement is moderate to massive
- ***Murmurs*** may be present.

## Eissenmerger's Syndrome

**465. Answer is A (Return of left ventricle and right ventricle to normal size):** *Ghai 6th/415; Braunwald 7th/1498*

*Eisenminger syndrome is associated with severe pulmonary arterial hypertension and right ventricular hypertrophy. The right ventricular size will certainly not return to normal once eisenminger syndrome develops.*

- ***Dilated central pulmonary arteries and rapid tapering of the peripheral pulmonary vasculature (pruning)*** *are the radiographic hallmarks of Eisenminger's syndrome' – Braunwald.*
  *'The hilar (central) area suggests pulmonary plethora whereas the peripheral lung fields suggets pulmonary oligemia' – Ghai 6th/415*
- 'Pulmonary hypertension develops due to pulmonary vascular obstructive disease affecting the 'pulmonary ***arteries***'. ***'Pulmonary vein'*** *will not be distended.*

## Miscellaneous

**466. Answer is A (ASD):** *see below ; Q.202 / AI 2002*

*ASD is the single best answer of exclusion.*

Cardiac anomalies in congenital rubella are mentioned differently in different books !

| | |
|---|---|
| According to GHAI | : PDA > PS> VSD |
| According to CPDT | : PDA > PS> VSD |
| According to Harrison | : PDA > PS> ASD |
| According to Nelson | : PDA > PS (ASD & VSD not mentioned) |

We have chosen ASD as the one to be excluded as both GHAI & CPDT mention VSD as a finding is cases of congenital rubella. Nevertheless Harrison mentions ASD as well, and so you are on your own, if you wish to differ.
*The commonest congenital cardiac anomaly is Congenital Rubella is PDA.*

**467. Answer is C (Renal Parenchymatous disease):** *Refer text below*

*Sustained severe hypertension in children is most commonly caused by Renal parenchymatous disease.*

**468. Answer is C (Assessment of child for presence of Heart disease):** *Ghai 5th / 294*

*NADA's criteria are used for assessment of child for presence of heart disease.*

*The assessment of a child for the presence or absence of heart disease can be done with the help of some guidelines suggested by NADA. These guidelines are called NADA's criteria.*

| Major | Minor |
|---|---|
| • Systolic murmur, grade III or more, especially with a thrill | • Systolic murmur < grade III |
| • Diastolic murmur | • Abnormal 2nd heart sound<br>• Abnormal ECG |
| • Cyanosis | • Abnormal X Ray |
| • Congestive cardiac failure | • Abnormal BP |

*Presence of one major and two minor criteria are essential for indicating the presence of heart disease.*

## Endocarditis

**469. Answer is C (Raised ESR):** *Harrison 18th /1055*

***Raised ESR is not part of diagnostic criterion for infective endocarditis. Positive Rheumatoid Factor (immunogenic phenomen) is a minor criteria while positive blood culture and positive echocardiogram are both major criterion for diagnosis of Infective Endocarditis.***

**The Duke Criteria for the Clinical Diagnosis of Infective Endocarditis:**

| Major Criteria |
|---|
| *1. Positive blood culture* |
| • Typical microorganism for infective endocarditis from two separate blood cultures<br>• Viridans streptococci, *Streptococcus gallolyticus*, HACEK group, *Staphylococcus aureus*, *or*<br>• Community-acquired enterococci in the absence of a primary focus, *or*<br>• Persistently positive blood culture, defined as recovery of a microorganism consistent with infective endocarditis from:<br>• Blood cultures drawn >12 h apart; *or*<br>• All of 3 or a majority of 4 separate blood cultures, with first and last drawn at least 1 h apart<br>• Single positive blood culture for *Coxiella burnetii* or phase I IgG antibody titer of >1:800 |
| *2. Evidence of endocardial involvement* |
| • ***Positive echocardiogram***[b]<br>• Oscillating intracardiac mass on valve or supporting structures or in the path of regurgitant jets or in implanted material, in the absence of an alternative anatomic explanation, *or*<br>• Abscess, *or*<br>• New partial dehiscence of prosthetic valve, *or*<br>• New valvular regurgitation (increase or change in preexisting murmur not sufficient) |
| **Minor Criteria** |
| 1. Predisposition: predisposing heart condition or injection drug use<br>2. Fever 38.0°C (100.4°F)<br>3. Vascular phenomena: major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, Janeway lesions<br>4. Immunologic phenomena: glomerulonephritis, Osler's nodes, Roth's spots, ***rheumatoid factor***<br>5. Microbiologic evidence: positive blood culture but not meeting major criterion as noted previously[c] or serologic evidence of active infection with organism consistent with infective endocarditis |

[a]Definite endocarditis is defined by documentation of two major criteria, of one major criterion and three minor criteria, or of five minor criteria.
[b] Transesophageal echocardiography is recommended for assessing possible prosthetic valve endocarditis or complicated endocarditis.
[c]Excluding single positive cultures for coagulase-negative staphylococci and diphtheroids, which are common culture contaminants, and organisms that do not cause endocarditis frequently, such as gram-negative bacilli.
***Note:*** HACEK, *Haemophilus* spp., *Aggregatibacter actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, *Kingella* spp.

**470. Answer is A (ASD):** *Harrison 14th/ 786, 16th/ (not elaborated); Harrison 17th/1460; API 8th/500; Harrison 18th/p 1923*

*Endocarditis is unusual in sites with a small pressure gradient as in – ASD – Harrison*

**Risk of infective endocarditis in various lesions**

| High Risk | Moderate Risk | Low Risk |
|---|---|---|
| • *Prosthetic heart valve*<br>• *Tetralogy of fallot*<br>• *PDA*<br>• *A regurgitation*<br>• *A stenosis*<br>• *Coarctation of Aorta*<br>• *VSD*<br>• *Mitral regurgitation* | • *MVP + M.R.*<br>• *T. Stenosis*<br>• *T. Regurgitation*<br>• *P. Stenosis*<br>• *M. Stenosis* | • *ASD*<br>• *MVP without MR* |

**Endocarditis tends to occur in**
- High pressure areas (left side of heart)
- Downstream from sites where blood flow at a high velocity through a narrow orifice from a high to a low pressure chamber (distal to constriction in coarctation of aorta)
- Endocarditis occurs more frequently in patients with valvularincompetance than in those with pure stenosis.

**471. Answer is A (Small ASD):** *Harrison 18th/1863; Harrison 17th/1460; API 8th/500*

*Endocarditis is unusual in sites with a small pressure gradient as in – ASD – Harrison*

**472. Answer is D (Ostium Secondum ASD):** *API 8th/500; Harrisons 16th/739; Repeat*

*Endocarditis is unusual in sites with a small pressure gradient as in ASD*
***ASD is low risk lesion for the development of infective endocarditis and the single best answer amongst the options provided***

**473. Answer is D (ASD) :** *API 8th/500; Harrisons 16th/739; Repeat copy above Answer 289*

*Endocarditis is unusual in sites with a small pressure gradient as in ASD*
***ASD is low risk lesion for the development of infective endocarditis and the single best answer amongst the options provided***

**474. Answer is D (ASD):** *API 8th/500; Harrisons 16th/739*

*Endocarditis is unusual in sites with a small pressure gradient as in ASD*
***ASD is low risk lesion for the development of infective endocarditis and the single best answer amongst the options provided.***

**475. Answer is D (ASD) :** *API 8th/500; Harrisons 16th/739; Repeat*

*Vegetations of infective endocarditis are least common with ASD amongst the options provided*

**476. Answer is A (ASD) :** *API 8th/500; Harrsions 16th/739: Repeat*

*Endocarditis is unusual in sites with a small pressure gradient as in ASD*
***ASD is low risk lesion for the development of infective endocarditis and the single best answer amongst the options provided***

**477. Answer is B (VSD):** *Ghai 6th/ 404*

*VSD is the most common congenital lesion to be complicated by infective endocarditis* – Ghai 6th/ 404

**478. Answer is B (Mitral regurgitation):** *See previous question*

*Amongst the choices provided only mitral regurgitation has been grouped as one with a high risk. All others are grouped as conditions carrying only a moderate risk.*

**479. Answer is A (Lung):** *Read text below*

*Mitral valve vegetation would obviously not go to the lung, as that would involve a 'backward flow'.*

**480. Answer is D (Tricuspid valve):** *Harrison 15th/ 811; 16th / 734; 17th/791* Harrison 18th/p 1055

*Most common heart valve involved in IV drug layers is tricuspid valve. 'In almost 50% of patients who have endocarditis associated with injection drug use, infection is limited to the tricuspid valve' – Harrisons 16th/ 734*

**Endocarditis in drug abusers:**

- most *common age of patients affected – young males*[Q]
- *most often source of infecting microorganisms is: skin*[Q]
- *most common agent is staphylococcus aureus*
- *most common valve involved is Tricuspid valve.*
- *tricuspid valve (50%) > aortic valve (25%) > mitral valve (20%) > multiple valves (rest)*
- *murmurs are* frequently absent[Q]

| |
|---|
| *Cardiac murmurs are almost always present in infective endocarditis except in patients with:*<br>- early acute endocarditis<br>- *intravenous drug abuse with tricuspid valve infection* |

**481. Answer is A (Septic Infarcts to lung):** *See previous question*

*Septic infarcts from the right side of the heart will first reach the lungs via the pulmonary artery due to normal forward flow.*

**482. Answer is C (Tip of palms and soles):** *Harrison 17th/791; Read text below* Harrison 18th/p 1054, 1055

*Oster's nodes are painful tender nodules in the pulp of fingers and soles, seen in patient of infective endocarditis.*

**Lesions seen in infective endocarditis that merit attention are :**

- **Osler's nodes :**
  - *Painful*[Q] tender pea size erythematous nodules *in the pulp of finger and sole.*
  - Occur in crops and
  - Indicate either an immunological phenomenon or emboli to distal digital arteries.
- **Janeway lesions**[Q]**:**
  - *Small maculopapular erythematous or hemorrhagic nontender*[Q] *lesions.*
  - *Commonly seen in palms and soles*[Q]
- **Roth's lesions**[Q]**:**
  - *Oval, retinal haemorrhages with a clear pale centre.*
- **Splinter hemorrhages**[Q]**:**
  - *Linear subungual dark red streaks*
  - *Commonly seen in fingers; less commonly in toes*[Q]

**483. Answer is A (Infective Endocarditis):** *Harrison 17th /791; Macleod's Clinical Examination 12th/327*

***Roth's spots (lesions) are oval retinal haemorrhages with a clear pale center that are typically seen in patients with subacute bacterial endocarditis. They are believed to be caused by immune complex deposition and are included as a minor criterion amongst Duke's criteria for clinical diagnosis of Infective Endocarditis.***

**Typical Named Lesions**
**Minor criteria for diagnosis of Infective Endo carditis (Duke's)**

| Vascular Phenomenon | Immunologic Phenomenon |
|---|---|
| • *Janeway's lesions*<br>Small maculopapular erythematous or hemorrhagic **non tender**[Q] lesions typically seen in palms & soles | • *Oster's nodes*<br>Painful[Q], tender[Q], pea size erythematous nodules in the pulp of fingers & soles<br>• *Roth's spots*<br>Oval retinal haemorrhages with a clear pale center (flame shaped haemorrhages with a central cotton wool spot) |

**484. Answer is C (Thrombus in left atria):** *Harrison 15th/ 811; Robbins 5th/ 552, Robbins 6th/ 574*

*Infective endocarditis does not lead to formation of thrombi within the left atrial. It may however lead to formation of friable vegetations that may embolize to the systemic circulation as infective emboli.*

Infective endocarditis is characterized by colonization or invasion of the heart valves or mural endocardium by a microbiological agent, leading to the formation of bulky, friable vegetations laden with organisms

**Cardiac complications**

| Valve | Mural / myocardium | Aorta |
|---|---|---|
| Valvular insufficiency<br>Valvular stenosis<br>↓<br>**Perforation of valve** | Myocardial ring a abscess<br>↓<br>Pericarditis (suppurative)<br>↓<br>**Perforation of interventricular septum or free myocardial wall** | **Perforation of the aorta** |

**485. Answer is C (Salmonella Typhi):** *Harrison 16th/732, 820, 830, 891, 899; Ananthnarayanan 7th/192, 200, 204, 212, http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=1998650&dopt=Abstract*

*Endocarditis is common with staphylococcus albus, streptococcus fecalis and pseudomonas aeruginosa.*
**Endocarditis has only been mentioned as rare complication of salmonella typhi infection.** – *Harrison 16th/899*

*The least likely organism to infective endocarditis amongst the options provided is salmonella typhi.*

**Other options**

| Staphylococcus albus (Staph. epidermis) (Coagulase Negative staph.) | Streptococcus fecalis (Enterococci) | Pseudomonas Aeroginosa Gram negative bacilli |
|---|---|---|
| • S. epidermis (albus) is the most Common coagulase negative staphylococii<br>• Coagulase negative staph (S. epidermidis/alba) are the *most common cause of 'Prosthetic valve endocarditis'* | • Streptococci fecalis is the *most common cause of enterococcal infective endocarditis*<br>• These organism account for 10 - 20% of cases of bacterial endocarditis | • *Common agent in endocarditis among infection drug users*<br>• P. aerug inosa infects the native heart valves of intravenous drug users as well as prosthetic heart valves |

**486. Answer is C (Staphylococcus Aureus):** *Harrison 18th/p 1053 Harrisons 17th/790, Harrisons 16th/732*

*The most common cause for infective endocarditis overvall is staphylococcus aureus*

Infective Endocarditis

| Native valve endocarditis | Prosthetic valve endocarditis | Endocarditis in IV Drug abusers |
|---|---|---|
| Most common cause is *Staphylococcus aureus*Q | *Most common cause is coagulose negative staphylococci*Q | *Most common cause is staphylococcus aurcus*Q |

*The most common cause (combined) for infective endocarditis from all causes is staphylococcus aureus*

**487. Answer is B (Staphylococcus Epidermidis):** *Harrison's 17th/ 790*

*The most common causative organisms of infective endocarditic within the first 12 months after valve surgery are Coagulase Negative Staphylococci.* ***Staphylococcus Epidermidis is a coagulase negative staphylococcus and the single best answer of choice.***

| Organism | Prothetic Valve endocarditis (% of cases) Time of onset after valve surgery | | |
|---|---|---|---|
| | < 2 months | 2-12 months | > 12 months |
| ***Coagulase Negative Staphylococcus*** | 33 | 32 | 11 |
| *Staphylococcus Aureus* | 22 | 12 | 18 |
| *Enterococcii* | 08 | 12 | 11 |
| ***Streptococcii (Viridans)*** | 01 | 09 | *31* |
| *Gram Negative Bacilli* | 05 | 06 | 08 |
| *Gram Negative Coccobacilii (HACEK)* | - | - | 06 |

**488. Answer is B (Staphylococcus):** '*Cardiothorocic Surgery' Oxford University Press; Harrison's 17th/ 790*

*Acute Infective Endocarditis with abscess formation is most commonly associated with staphylococcus.*

*'The most common organism causing acute infective endocarditis overall is staphylococcus aureus. Staphylococcus aureus endocarditis is particularly virulent and associated with annular and myocardial abscess formation and a higher mortality' – 'Cardiothorocic surgery' Oxford 2012/80*

*Paravalvular abscesses in patients with acute infective endocarditis is especially seen in association with virulent organisms like staphylococci and enterococcii. Such abscesses may also be seen in association with some virulent strains of streptococcal endocarditis.* ***Staphylococcus however are the most common organisms associated with such abscesses.***

**489. Answer is C (3 culture sets separated by at-least 1 hour over 24 hours):** *Harrison's 18th/ 1056*

*Three culture sets separated from one another by at-least 1 hour should be obtained over 24 hours.*

*'In the absence of prior antibiotic therapy three (2-bottled) culture sets separated from one another by at-least 1 hour should be obtained from different venepuncture sites over 24 hours. If the cultures remain negative 48 to 72 hours, two or three additional blood culture sets should be obtained' – Harrison 18th/ 1056*

**490. Answer is D (Coarctation of Aorta):** *Harrisons 16th/739*

*Coarctation of Aorta is a high risk cardiac lesion for the development of infective endocarditis and an indication for antibiotic prophyloxis.*

Prophylaxis for infective Endocarditis

| Cardiac lesion for which Endocarditis Prophylaxis is advised (moderate/High risk lesions) | |
|---|---|
| High Risk | Moderate Risk |
| • Prosthetic heart valves<br>• Prior bacterial endocarditis<br>• Complex cyanotic congenital heart disease; other complex congenital lesion after correction (see text)<br>• Patient ductus arteriosus<br>• ***Coarctation of the aorta***<br>• Surgically constructed systemic-pulmonary shunts | • Congenital cardiac malformations (other than high -/low-risk lesions), ventricular septal defect, bicuspid aortic valve<br>• Acquired aortic and mitral valve dysfunction<br>• Hypertrophic cardiomyopathy (asymmetric septal hypertrophy)<br>• Mitral valve prolapse with valvular regurgitation and/or thickened leaflets |

| Cardiac lesion for which Endocarditis Prophylaxis is not advised (Low risk lesions) |
|---|
| • Isolated secundum ASD<br>• Surgically repaired ASD, VSD, PDA (without residual defect, >6 months after repair)<br>• Prior coronary artery bypass graft<br>• Mitral valve prolapse without regurgitation or thickened leaflets<br>• Physiologic or functional murmur<br>• Prior Kawasaki disease or acute rheumatic fever without valve dysfunction<br>• Cardiac pacemakers or implanted defibrillators |

**491. Answer is A (Amoxycillin):** *Harrisons 16th/739*

*Amoxycillin is the standard drug of choice for antibiotic prophyloxis for oral cavity procedures in adults at moderate or high risk of infective endocarditis.*

Antibiotic Regimen for Prophylaxis of endocarditis in adults (Moderate/high risk)

| Oral Cavity Procedures<br>Respiratory Tract Procedures<br>Esophageal procedure |
|---|
| ↓ |
| Standard Regimen (Preferred Drug) |
| ***Amoxycillin***<br>*Ampicillin may be used parentrally (IV/IM) if patient is unable to take oral medications* |
| Patient with Penicillin Allergy |
| Clarithromycin<br>Cephalexin or Caphadroxil<br>Clindamycin<br>*(Cefazolin may be used parentrally (IV/IM) if patient is allergic to penicillin and unable to take oral medications* |

| Genitourinary Tract procedure<br>Gastrointestinal Tract procedure | |
|---|---|
| ↓ | |
| High Risk Patient | Moderate Risk Patient |
| ↓ | ↓ |
| Standard Regimen | Standard Regimen |
| Ampicillin (IV/IM)+Gentamycin | Amoxycillin (P.O) (or Ampicillin) |
| Patient with penicillin Allergy | Patient with penicillin Allergy |
| Vancomycin (IV) + Gentamycin | Vancomycin (IV) |

**492. Answer is D (Good Prognosis with treatment):** *Color Atlas of Infective Endocarditis (Springer) 2007/ 103*

*Fungal endocarditis is associated with a Poor Prognosis.*

**Fungal Endocarditis**

- Candida (Most common) and Aspergillus are the two most important causes of fungal endocarditis particularly in patients with prosthetic valves, suppressed immunity, or IV drug abuse.
- Current antifungal agents will not cure fungal endocarditis except in rare cases
- Combined medical and surgical treatment should be employed.

> Medical treatment: Amphotericin B± flucytosine
> Surgery (Radical debridement) should be performed early after commencing treatment, especially in patients with large vegetations, evidence of emboli, poor response to treatment, Aspergillus endocarditis and in those with prosthetic valves, since mortality is unacceptably high with treatment with antimycotic agents alone

- Antifungal drug treatment should be continued for life in patients with Prosthetic valve fungal endocarditis

**493. Answer is A (Infective endocarditis):** *Repeat; Refer text below: Robbins 8th/566,567,568; Harsh Mohan 6th/447; Paediatric Pathology by Stocker and Dehner (Lippincott) 2nd (2001)/552*

***Most friable vegetations with the highest risk of embolization are seen in infective endocarditis.***

| ***Friability of Vegetation and risk of embolization*** |
|---|
| ***Infective Endocarditis > NBTE (Marantic) > Rheumatic endocarditis and Libman Sack's endocarditis*** |

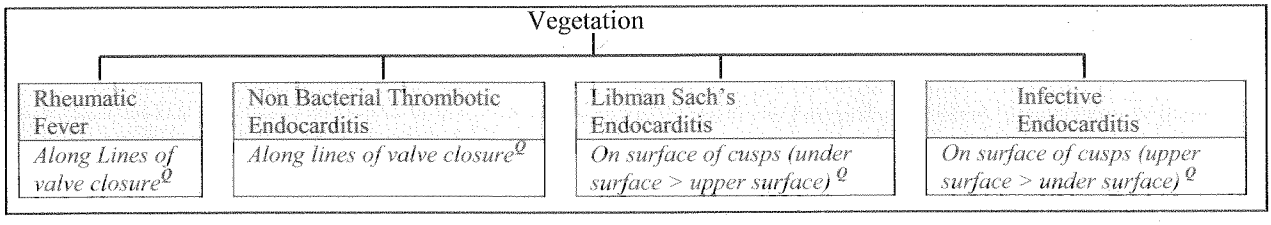
| Rheumatic Fever | Non bacterial Thrombotic (Marantic Endocarditis) | Libman Sack's Endocarditis (SLE) | Infective Endocarditis |
|---|---|---|---|
| • Small<br>• Warty, verrucous<br>• Usually Firm<br>May be friable (but less than those of NBTE)<br>(embolization rare) | • Small (but larger than those of rheumatic)<br>• Friable<br>(embolization common) | • Medium sized(small)<br>• Flat, Verrucous,Irregular<br>• Usually Firm; occasionally friable<br>(embolization rare) | • Large, Bulky<br>• Irregular<br>• Friable *(most friable)*[Q]<br>(embolization common) |
| • Along lines of closure | • Along lines of closure | • On surface of cusps<br>Both surfaces may be involved most common being the undersurface, less often on mural endocardium<br>• In pockets of valves | • Irregular vegetations on valve cusps that can extend onto the chordae.<br>• Less often on mural endocardium |
| • Sterile (no organisms) | • Sterile | • Sterile | • Non-sterile (bacteria) |
| • Non destructive<br>Valve perforation : no<br>Mural involvement: rare | • Non destructive<br>Valve perforation : no<br>Mural involvement: rare | • Destructive<br>Valve perforation : no<br>Mural involvement: common | • Destructive<br>Ulcerates or perforates underlying valve (or myocardium) |
| • Seen in Rheumatic fever | • Seen in hyper coagulable states e.g. cancer, promyelocytic leukemia increased estrogenic state | • Seen in SLE | • Seen in Infective endocarditis |

***Most common site:***

- ***Most common site*** *for vegetations in Libman Sack's endocarditis are the A-V values, mitral and tricuspid.*
- ***Most common site*** *for vegetations in NBTE is mitral and less often aortic and Tricuspid.*
- ***Most common site*** *for vegetations of RF is mitral followed by combined mitral and aortic.*

**494. Answer is B (Libman Sacks Endocarditis):** *Refer text above*

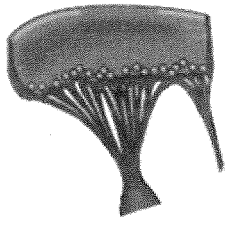
*Vegetation on under-surface of AV valves are typically seen in Libman Sacks Endocarditis (SLE).*



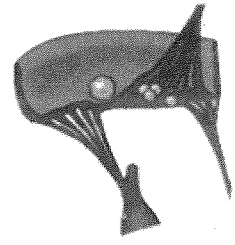

**495. Answer is C (Libman Sacks Endocarditis):** *Repeat*

***Verrucous vegetations on the surface of mitral valve cusps are typical of Libman-Sacks Endocarditis.***
***Libman Sacks Endocarditis is also known as Atypical Verrucous endocarditis (Dorland's)***
*Verrucous (wart like) vegetations are typically seen in Rheumatic Fever and Libman-Sacks Endocarditis. In rheumatic fever these are typically located along the lines of closure while in Libman-Sacks endocarditis they are usually located on the* ***surface of cusps*** *(commonly under-surface).*

| **Typical Verrucous endocarditis of acute RF** |
|---|
| *Tiny Small sterile verrucous vegetations along lines of closure* |



| **Atypical Verrucous endocarditis (Libman-Sacks)** |
|---|
| *Medium sized (or small) sterile verrucous vegetations on the surface of valve cusps* |



**496. Answer is A (SLE):** *Repeat; Refer text below: Robbins 8th/566,567,568; Harsh Mohan 6th/447; Paediatric Pathology by Stocker and Dehner (Lippincott) 2nd (2001)/552*

***Libman Sack's Endocarditis is seen in Systemic Lupus Erythematosis (SLE).***

**497. Answer is B (Libman sach's Endocarditis) :** *Robbins 6th/575; Robbins 7th/517; Harsh mohan 4th /302; Refer previous question*

***Flat vegetation in pockets of valves are charachteristic of Libman sach's endocarditis***

**498. Answer is A (Along line of closure of valves) :** *Robbins 7th/597*

***Rheumatic heart disease is charachterized by vegetations along lines of closure of valves***

**499. Answer is A (Rheumatic Heart Disease) :** *Robbins 6th/ 575; Robbins 7th /597; Harshmohan 4th/302*

***Firm warty vegetations along lines of closure of valves are charachteristic of Rheumatic Heart disease***

## Cardiac Involvement in Carcinoid Syndrome & SLE

**500. Answer is A (Pulmonary valve):** Harrison 18th/p 3062 *Harrison 17th/2351*

***Carcinoid syndrome most frequently involves the ventricular aspect of the tricuspid valve.***

Cardiac manifestations of carcinoid syndrome

- Cardiac disease is due to involvement of endocardium by dense fibrous deposits
- Cardiac disease primarily involves the right side (although left side lesions may also occur)
- The most commonly involved valve is tricuspid valve (ventricular surface/under surface)
- The second most commonly involved valve is pulmonary valve
- Predominant vavular lesion due to involvement of tricuspid valve is tricuspid regurgitation (valve is fixed open)
- Predominant valvular lesion due to involvement of pulmonary valve is pulmonic stenosis (valve is constricted)
- Most patients with cardiac lesion develop heart failure (80%)

**501. Answer is A (Fibrous endocardial thickening of Right ventricle, Tricuspid valve & Pulmonary valve):** *Robbins 7th/599, Braunwald 8th/297, Hurst 11th/2092; 'Pathology Pre test' 11th/211*

*Fibrous enodocardial thickening involving the right ventricle, tricuspid valve and pulmonic valve is the charachteristic pathological finding in carcinoid heart disease.*

**Carcinoid Heart Disease**

- Carcinoid heart disease is the cardiac manifestation of systemic syndrome caused by carcinoid tumors and results primarily from the bioactive products elaborated by carcinoid tumors at other sites.
- *Cardiac involvement predominantly* ***affects the endocardium and valves on the right side of heart***$^{Q}$ *(because bioactive tumor substances are inactivated by the lung) and* ***usually occurs in patients with hepatic metastasis***$^{Q}$ *(This bypasses the inactivation by the liver & exposes right heart to high levels of bioactive products)*
- This consists of firm plaque like (endocardial) fibrous thickening of the right ventricle tricuspid and pulmonic valves composed predominantly of ***smooth muscle cells and sparse collagen fibres***$^{Q}$, embedded in an acid mucopolysacharide rich matrix material. ***Elastic fibres are not present.***
- **Right sided cardiac lesions** are common and include involvement of the tricuspid valve, pulmoary valve and the right ventricular endocardium.

| Charachteristic Cardiac Lesions in Carcinoid Heart Disease (Right side of Heart) | |
|---|---|
| • Tricuspid valve thickening | ***Tricuspid Regurgitation is the primary lesion*** <br> ***Tricuspid stenosis is minimal*** |
| • Pulmonic valve thickenning | *Pulmonic Regurgitation (variable degree)* <br> *Pulmonic stenosis (variable degree)* |
| • Right ventricular endocardial thickening | *Restrictive cardiomyopathy may be seen* |

- **Left sided cardiac lesions** are uncommon but may be seen when blood containing the responsible mediator enters the left heart in certain specific circumstances.
  - Incomplete inactivation in lung due to very high blood levels
  - Incomplete inactivation due to '*right to left*' intra-cardiac shunt from a patent foramen ovale
  - Pulmonary carcinoid /pulmonary metastasis

**Note:**
*Endocardial thickening of Tricuspid valve with Tricuspid stenosis may be seen, but is not a charachteristic feature of carcinoid heart disease. The charachteristic valvular pathology affective the tricuspid valve is tricuspid valve regurgitation.*
*'Tricuspid stenosis is usually minimal'- Braunwald 8th/297; 'Pure tricuspid stenosis is rare' – Essentials of Anatomic Pathology 2nd/21-8*

**502. Answer is B (Tricuspid valve):** *Harrison 17th/235*

*The most commonly involved valve in carcinoid syndrome is tricuspid valve.*

**503. Answer is C (Tricuspid Regurgitation):** *Harrison 18th/ 3062*

*Carcinoid syndrome most frequently involves the ventricular aspect of the tricuspid valve.* ***The predominant lesion due to involvement of the tricuspid valve is Tricuspid regurgitation.***

**504. Answer is B (Tricuspid Regurgitation):** *Harrison 18th/p 3062; Harrison 17th/2351*

*Carcinoid syndrome most frequently involves the ventricular aspect of the tricuspid valve and leads to Tricuspid Regurgitation*

**505. Answer is B (Inflow tract of RV):** Harrison 18th/p 3062 *Harrison 17th/2351; Refere previous question*

*The most commonly involved valve in carcinoid syndrome is tricuspid valve which forms the inflow tract of Right ventricle.*

| | |
|---|---|
| Most commonly involved part of heart | : Inflow tract of RV (Tricuspid valve) |
| Second most commonly involved part of heart | : Outflow tract of RV (Pulmonic valve) |

**506. Answer is B (Pericarditis):** *Harrison 18th/ 2729*

*The most common presentation of cardiac involvement in lupus is pericarditis.*

*The most common cardiac abnormality in patients with Systemic Lupus Erythematosus (SLE) is Pericarditis*

## Sudden Cardiac Death

**507. Answer is D (Ventricular septal defect):** *Harrison 16th/1619; Harrison The Eisenmenger Syndrome in Adults': http"//www.annals.org/cig/content/full/128/9/745 May 1998/Volume 128 Issue 9/Pages 745-755*

*Amongst the options provided ventricular septal defect is the least likely diagnosis to result in sudden cardiac death.*

- **Hypertrophic and Dilated Cardiomyopathy :**
  The cardiomyopathies (Hypertrophic and Dilated) are the second most common category of diseases associated with risk of 'Sudden cardiac death'.- *Harrison 16th/1620*
- **Eisenmenger's Syndrome :**
  *"Most patients with the Eisenmenger's syndrome die of 'sudden cardiac death', probably from a ventricular arrythmia." The Eisenmenger Syndrome in Adults':http"//www.annals. org/cig/content/full/128/9/745 May 1998/Volume 128 Issue 9/Pages 745-755*
- **Ventricular septal defect :**
  The occurance of sudden cardiac death in cases of isolated ventricular septal defect has not been emphasized in literature. Sudden death may probably be seen in early childhood but only isolated case reports have been documented. ***VSD therefore is the least likely diagnosis and hence the answer of exclusion.***-*J Paediatr Child Health. 1994 Oct;30(5):439-40*

**Caridac Arrest and Sudden Cardiac Death**

| Structural Causes | Functional Contributing Factors |
|---|---|
| I. Coronary heart disease | I. Alterations of coronary blood flow |
| A. Coronary artery abnormalities | A. Transient ischemia |
| 1. Chronic atherosclerotic lesions | B. Reperfusion after ischemia |
| 2. Acute (active) lesions (plague fissuring, platelet aggregation, acute thrombosis) | II. Low cardiac output states |
| 3. Anomalous coronary artery anatomy | A. Heart failure |
| B. Myocardial infarction | 1. Chronic |
| 1. Healed | 2. Acute decompensation |
| 2. Acute | B. Shock |
| II. Myocardial hypertrophy | III. Systemic metabolic abnormalities |
| A. Secondary | A. Electrolyte imbalance (e.g., hypokalemia) |
| B. ***Hypertrophic cardiomyopathy*** | B. Hypoxemia, acidosis |
| 1. Obstructive | IV. Neurophysiologic disturbances |
| 2. Nonobstructive | A. Autonomic fluctuations: central, neural, humoral |
| III. ***Dilated cardiomyopathy – primary muscle disease*** | B. Receptor function |
| IV. Inflammatory and infiltrative disorders | V. Toxic responses |
| A. Myocarditis | A. Proarrhythmic durg effects |
| B. Noninfectious inflammatory diseases | B. Cardiac toxins (e.g. cocaine, digitalis intoxication) |
| C. Infiltrative diseases | C. Drug interactions |
| D. Right ventricular dysplasia | |
| V. Valvular heart disease | |
| VI. Electrophysiologic abnormalities, structural | |
| A. Anomalous pathways in Wolff-Parkinson-White syndrome | |
| B. Conducting system disease | |
| VII. Inherited disorders of molecular structure associated with electrophysiologic abnormalities (e.g., congenital long QT syndromes, Brugada syndrome) | |

## Miscellaneous

**508. Answer is D (Generates impulses at the highest rate):** *Ganong 22nd/547; 21st/ 549; Guyton 10th/ 111*

*"The sinus node controls the beat of the heart because its rate of discharge is greater than that of any other part of the heart. Therefore the sinus node is the pacemaker of the heart" - Guyton*

*Although the AV node and Purkinje fibres are also capable of generating impulses spontaneously, it is the sinus node which controls the hearts rhythmicity and acts as the pacemaker of the heart.*

*This is attributed to the fact that the discharge rate of the SA node is considerably faster than the natural self excitatory discharge of either the AV node or the Purkinje fibres. Each time the sinus node discharges its impulse is conducted into both, the AV node and Purkinje fibres and discharges their excitable membranes. Then these tissues as well as the sinus node recover and start almost at the same time, but the sinus node discharges again much more rapidly and discharges the AV node & Purkinje fibres again before they can reach their own threshold for self excitation.*

**Rhythmicity of Heart**

| Tissue | Rate of impulse generation |
|---|---|
| SA node | 70-80/minutes *(Highest)*$^{Q}$ |
| AV node | 40-60/minutes |
| Bundle of His | 40/minutes |
| Purkinje system | 24/minutes |

Rate of impulse generation to decreasing order:
*SA node*$^{Q}$ **> AV node > Bundle of His >** *purkinje system*$^{Q}$

***AV node* and *purkinje fibres* are also capable of generating impulses spontaneously but SA node discharges most rapidly (70-80/min) & depolarizes the AV node and purkinje fibres before they can reach their own threshold for self excitation.**

**509. Answer is A (SA Node):** *Refer previous question; Ganong 22nd/549; Gyuton 10th/111*

*The rate of impulse generation/rate of discharge is highest in the SA node.*

**Note:**

| | | |
|---|---|---|
| Highest Rate of impulse generation in seen in | : | SA Node$^{Q}$ |
| Highest Rate of conduction is seen in | : | Purkinje System$^{Q}$ |

**510. Answer is D (Purkinje System) :** *Ganong 20th / 530 (table 28-1)*

*Purkinje system has the highest conduction speed in cardiac tissue.*

**The conduction rate of various cardiac tissues:**

| Tissue | Conduction rate (m/s) | Relative value |
|---|---|---|
| S A node | **0.05** | *2nd least* $^{Q}$ |
| AV node | **0.02 – 0.05** | *Least* $^{Q}$ |
| **Atrial pathway** | **1** | |
| **Bundle of His** | **1** | |
| **Ventricular muscle** | **1** | |
| Purkinje system | **4**$^{Q}$ | *Highest*$^{Q}$ |

**511. Answer is D (Purkinje System):** *Ganong 22nd/549*

*Purkinje fibers has fastest conduction*$^{Q}$

**512. Answer is A (AV node):** *Ganong 22nd/547-549; NMS Physio 4th/139*

*Minimum conduction velocity is seen in AV node.*

Conduction Rate in decreasing order:
*Purkinje fibers* $^{Q}$ **> Bundle of His = Ventricular muscle = Atrial pathway> SA node >** *AV node*$^{Q}$

| Tissue | Conduction rate (m/s) | Relative value |
|---|---|---|
| S A node | **0.05** | *2nd least* $^{Q}$ |
| AV node | **0.02 – 0.05** | *Least* $^{Q}$ |
| **Atrial pathway** | **1** | |
| **Bundle of His** | **1** | |
| **Ventricular muscle** | **1** | |
| Purkinje system | **4**$^{Q}$ | *Highest*$^{Q}$ |

**513. A i.e. Septum – Endocardium – Epicardium:** *Ganong 22nd/ 549, 550*

*Activation preads from septum to endocardium to epicardium*

**Order of Activation of Ventricular Muscle**

First the ***Purkinje system*** inside the ***septum***$^{Q}$

↓

Entire ***Endocardium***$^{Q}$ of ventricle

↓ *through ventricular muscle*

***Epicardium***$^{Q}$

**514. Answer is D (Right bundle branch) :** *Snell's 7th/119-120*

*Right bundle is supplied by the Left coronary artery.*

*Right coronary artery supplies the SA node (in 65% cases), AV node, AV bundle or Bundle of His and part of left bundle branch(LBB)*

*Left cronoary artery supplies the right bundle branch (RBB, part of LBB and sometimes the SA node (in 35% cases),*

**Conducting system of the heart consists of**

- **SA Node** — *Usually supplied by the* ***Right coronary artery*** (SA node is sometimes supplied by the left coronary artery)
- **AV Node** — *Right coronary artery*
- **AV bundle or bundle of His** — *Right coronary* artery
  - **Right bundle branch** — *Left coronary artery*
  - **Left bundle branch** — Right and Left coronary arteries

→ **Purkinje Fibres**

**515. Answer is B (Left dominance):** *Snell's 8th/113-114; BDC 4th Vol I/251*

*When the posterior interventricular artery is derived from the circumflex artery (br. of left coronary artery) the circulation is described as 'left dominant'*

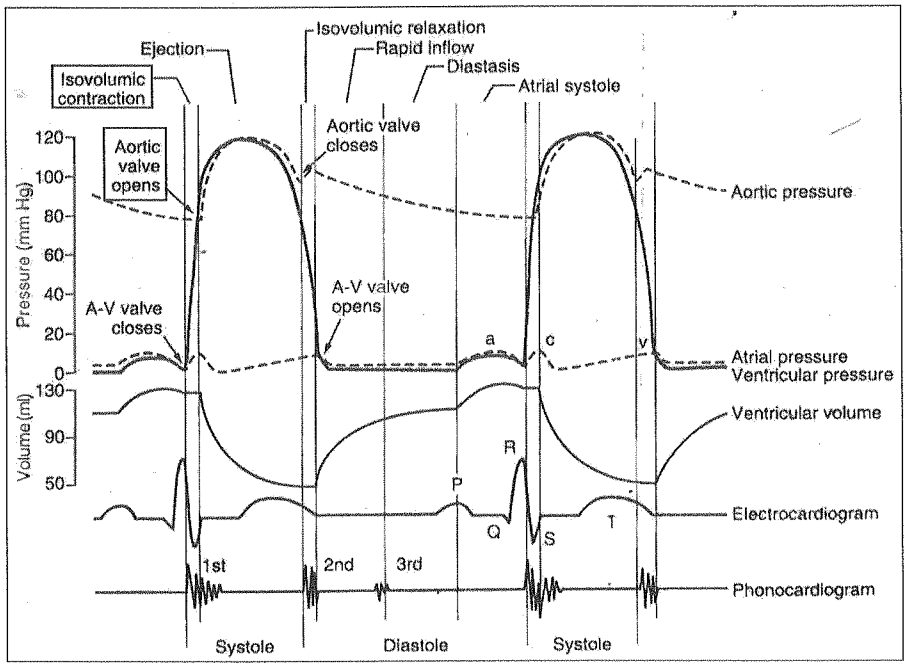
**Dominance of the coronary arterial system**

Dominance of the coronary arterial system is determined by the coronary artery (Left or Right) which gives rise to the posterior interventricular artery.

| Right Dominance (more common) | Left Dominance (Less common) |
|---|---|
| *Posterior interventricular artery is derived from the Right Coronary Artery* | ***Posterior interventricular artery is derived from the Left Coronary artery (circumflex branch)*** Note: *Circumflex artery is the continuationof Left coronary artery.* |

**516. Answer is B (End of isovolumetric contraction) :** *Guyton 10th / 99*

*The Aortic valve opens at the end of isovolumic contraction.*




***The period of isovolumetric contraction*** *is when ventricle contracts as a closed chamber with both the semilunar and AV valves closed.*

*The total period of isovolumetric contraction lasts about .05 sec until the pressure in the left and right ventricle exceeds the pressure in the aorta and the aortic and pulmonary valves open.*

**Note from figure above :**

| | |
|---|---|
| Beginning of systole$^{Q}$ | AV valves close |
| End of isovolumetric contraction$^{Q}$ | Semilunar valves open |
| End of diastole$^{Q}$ | AV valves close |
| End of diastasis$^{Q}$ | AV valves are open and semilunar valves are closed |

**517. Answer is A (Atrio-ventricular valves open):** *Guyton 10th/99; Refer previous question*

*AV valves open at the end of isovolumetric relaxation.*

**AV valves open:**

*At the end of iso-volumetric relaxation phase, AV valves open, so as to allow blood to flow rapidly into ventricles (ventricular filling phase).*

**AV valves close:**

*AV valves close at the begining of iso-volumetric relaxation.*

**Peak of C wave on JVP:**

*Peak of 'c' wave corresponds to the end of iso-volumetric contraction.*

**T wave in JVP**

*'T' waves in ECG begin slightly before the end of ventricular contraction and end with the end of iso-volumetric relaxation phase.*

**518. Answer is C (Both valves are closed)**

*During isovolumetric contraction the ventricle contracts as a closed chamber with both the semilunar and AV valves closed (All valves are closed)*

**519. Answer is B (Opening of A-V valves):** *Ganong Review of Medical Physiology 22/e P- 565-666; Chaudhuri Concise Medical Physiology 5/e P- 176; Sembulingum Essentials of Medical Physiology 3/e P- 436; Repeat*

*Isovolumetric Relaxation phase ends with opening of the Av valves (Refer figure)*

| Valvular event (valves) | Cardiac events | ECG | JVP (Jugular venous Pressure curve) |
|---|---|---|---|
| ***Opening of AV valve*** $^{Q}$ | ***End of isovolumic relaxation phase*** $^{Q}$ | ***End of T wave*** $^{Q}$ ***(phase b/w T wave and new p wave)*** | ***V-Y descent*** $^{Q}$ |
| Closure of AV valve | - End of diastole<br>- Beginning of isovolumic contraction | Later half of R wave | End of 'x' descent |
| Opening of semilunar valve | *End of isovolumic contraction* $^{Q}$ | ST segment | Peak of 'C' wave |
| Closure of semilunar valve | - Beginning of isovolumic relaxation phase<br>- Beginning of diastole | Later half of T wave | |

**520. Answer is B (3.2):** *Ganong 20th/550; Guyton 10th/210*

*The cardiac index in a normal person is approximately 3.2 L/min/m²*

$$\textbf{Cardiac Index} = \frac{\text{Cardiac Output}}{\text{Body Surface Area}} = \frac{5}{1.7} = 3\text{L / min /m}^2$$

**521. Answer is B (Mean Stroke Volume) :** *Ganong 20th / 550; Guyton 10th / 210*

*Mean stroke volume is the amount of blood pumped out of each ventricle per beat. It is calculated as the cardiac output in L/min divided by the heart rate.*

$$\text{Mean Stroke Volume} = \frac{\text{Cardiac Output}}{\text{Hear Rate}}$$

| Parameter | Definition | Value |
|---|---|---|
| *Cardiac output* | The output of the heart per unit time | *5L/min* $^{Q}$ |
| *Stroke volume* | The amount of blood pumped out of each ventricle per beat.<br>***Mean stroke volume*** $^{Q}$ ***= Cardiac output/Heart rate*** | *70 ml* $^{Q}$ |
| Cardiac Index | *Cardiac output/ body surface area* $^{Q}$ | *3.2L/min/m²* $^{Q}$ |

**522. Answer is D (Diastole + 1/3rd Pulse pressure) :** *Chaudhary 2nd / 244; Chaudhary 5th/244*

*Mean arterial pressure can be measured as Diatolic BP + 1/3 Pulse Pressure*

*Mean arterial pressure is the 'weighted' mean pressure of the blood.*
*In a cardiac cycle, the systole lasts for about 0.3 sec and diastole for about 0.5 sec. Therefore in a subject having a cardiac cycle of 0.8 sec, the mean BP cannot be taken as (systole + diastole)/2 mmHg but instead a weighed mean (in which duration of systole and diastole are taken care of) is required.*

| *Calculations for Mean Blood Pressure* |
|---|
| ***Mean BP = Diastolic BP + 1/3rd Pulse pressure*** $^{Q}$ |
| *Mean BP = Diastolic BP + 1/3rd (Systolic BP – Diastolic BP)* $^{Q}$ |
| $\textbf{Mean BP} = \frac{1}{3}$ ***(Systolic BP + 2 Diastolic BP)*** |

**523. Answer is A (SBP + 2DBP)/3:** *Chaudhary 2nd / 244; Chaudhary 5th/244*

*Mean arterial pressure can be measured as (SBP+2DBP/3)*

**524. D i.e. Peripheral resistance x cardiac output:** *Ganong 22nd/590*

*Blood pressure is defined as the product of cardiac output and peripheral resistance.*

| Blood pressure = | **Cardiac output x peripheral resistance** $^{Q}$ **or Blood flow (Q) x resistance (R)** |
|---|---|

**525. Answer is C ($kP_a$):** *Taber's Cyclopedic Medical Dictionary / 2216 ; Ganong 18th / 54*

*Pressure in SI units is measured in Pascal [Pa]*
*Blood pressure in SI units is measured in kPa.*

**526. Answer is B (Is higher than intraarterial pressure):** *Ganong 22nd/ 590 , Medicine for Anaesthetists 4th/ 285 Screening for Diseases by Snow (2004) /135]*

*Blood pressure measured by Sphygmomanometer with a standard cuff tend to overestimate 'true' arterial pressures as measured by arterial cannulation, especially in the elderly and the obese* – Ganong.

**Blood pressure Measurement with Sphygmomanometers**

- Sphygmomanometer is a device that measures blood pressures indirectly.

  External pressure is applied with a sphygmomanometer cuff to the overlying tissues and the pressure required to occlude the artery is assumed to be equal to the intra arterial pressure.

- The sphygmomanometer will give accurate readings only if no pressure (zero mm. of mercury) is dissipated in compressing the soft tissues overlying the artery.

  *However in practice, some pressure is always dissipated in compressing the blanket of soft tissues overlying the artery and hence* ***blood pressure measured by the sphygmomanometer are slightly higher than true intra arterial pressures.***

- The amount by which the sphygmomanometer overestimates the true blood pressure is influenced by the amount of overlying fat and the compressibility of the vessles.

**Sources of Error**
Blood Pressure measured by Sphygmomanometer

| Overlying Soft tissue Blanket | Compressibility of vessels | Size of Cuff |
|---|---|---|
| • Thick overlying soft tissue blanket leads to overestimation of blood pressure<br>• *Obese individuals*$^{Q}$ have a thick blanket of fat which dissibates cuff pressure. Hence Blood pressure is likely to be overestimated when measured by sphygmomanometer and a standard cuff. | • Vessels that are difficult to compress lead to overestimation of blood pressure<br>• Blood pressure measured in such individuals with sphygmomanometer will result in over estimation of blood pressure (Pseudohypertension)<br>• Such Patients include *Elderly individuals, diabetics*$^{Q}$ *and patients who* may have rigid sclerotic vessels that are difficult to compress (*Mokenberg's asteriosclerosis*). | • *Small (Narrow) cuff*$^{Q}$ leads to falsely high blood pressure recordings (overestimation)<br>*Large (wide) cuff*$^{Q}$ leads to falsely lower blood pressure recordings (under estimation)<br>• If the standard arm cuff is used to measure blood pressure in the thigh falsely high blood pressure values will be obtained (due to relatively smaller cuff size and greater soft tissue blanket).<br>• If the standard arm cuff is used on the forearm falsely lower blood pressure values may be recorded. |

Note
- *More accurate pressure can be recorded in obese individuals by using a wider cuff size*$^{Q}$
- *More accurate pressure can be recorded in the thigh by using a wider cuff size*$^{Q}$

**527. Answer is B (Diastolic BP is indicated by 4th Kovotkoff's sound):** *Ganong 22/ 589-90;Snow Screening for disease (2004) /135; Medicine for anesthesia 4th/285; Guyton 11th/166-67,175-76*

*Diastolic blood pressure is indicated by the 5th fourth Korotkoff sound (not by fourth Korotkoff sound).*

**Diastolic blood pressure is best indicated by fifth Korotkoff sound**

**Korotkoff sounds are produced by turbulent flow in artery**

| | | |
|---|---|---|
| 1. | Faint, clear, tapping sounds | It indicates ***systolic BP***$^{Q}$ |
| 2. | Murmur / swishing sounds | |
| 3. | More intense, crisper sounds | |
| 4. | Distinct abrupt muffled f sounds | *Indicates diastolic BP in children.* |
| 5. | No sound | ***Best correlates with diastolic BP in normal adults***$^{Q}$. |

**Cuff width should be 40% of arm circumference**

*Appropriate Cuff size*

- Ratio of width of compression cavity of cuff (bladder) to circumference of extremity is of critical importance. According to American Heart Association

Bladder **width** ***should be 40% of circumference or 1.2 times of diameter of extremity***$^{Q}$

Bladder **length** should be ***80% of arm circumference***$^{Q}$

**Length to width ratio is 2 : 1**

**Small cuff measures spuriously elevated Diastolic blood pressure and Monkenberg sclerosis causes pseudohypertension**

| False High values are found in | False low values are found in |
|---|---|
| **Thick overlying Soft tissue blanket**<br>• *Obese individuals*$^{Q}$<br>**Limited Compressibility of vessels**<br>• *Elderly*<br>• *Atherosclerosis*<br>• *Diabetics*<br>• *Mokenberg's arteriosclerosis*<br>**Size of cuff**<br>• Small narrow cuff | Large (wide) cuff eg standard arm cuff used in forearm.<br>Too fast Deflation rate leads to too low systolic pressure.<br>Improper interpretation of Auscultatory gap<br>It is the interval of pressure where Korotkoff's sounds indicating true systolic pressure fade away and reappear at a lower pressure. The improper interpretation of this gap may l/t errors made in falsely low recording of systolic BP. It usually occurs at high pressures, when there is silence at pressures greater than systolic BP, except that the pulse can still be palpated. |

**528. Answer is A (Auscultatory gap):** *Ganong 22nd/590; Chaudhuri Concise Medical Physiology 5th/210*

***Spuriously high BP may be seen in obese individuals with a thick blanket of fat which dissibates cuff pressure, patients with thick calcified vessels and use of small narrow cuff.***

**529. The Answer is B (more than intravascular pressure) :** *Ganong 22nd/ 590 , Medicine for Anaesthetists 4th/ 285 Screening for Diseases by Snow (2004) /135; Bijlani 1st / 189 ; Ganong / 20th 568*

*Blood pressure measured by Sphygmomanometer with a standard cuff tend to overestimate 'true' arterial pressures as measured by arterial cannulation, especially in the elderly and the obese – Ganong*

**530. Answer is D (These may result in aneurysm):** *Robbins 7th/575*

*Ventricular aneurysms result from transmural infarcts, which involve the whole thickness of myocardium from epicardium to endocardium.* ***Subendocardial infarcts being limited to only the inner one third or at most one half of the ventricular wall do not cause ventricular aneurysms.***
*Aneurysm of the ventricular wall most commonly results from a large transmural anteroseptal infarct'- Robbins*

| Transmural infarcts | Subendocardial infarcts |
|---|---|
| • Ischaemic necrosis involves the full or nearly full thickness of ventricular wall.<br>(Myocardium from epicardium to endocardium is involved)<br>• Associated with coronary atherosclerosis acute plaque change and superimposed thrombosis. | • Ischaemic necrosis involves the inner one third or at most one half of the ventricular wall.<br>(Epicardium is not involved)<br>• Associated either with atherosclerosis, plaque changes and thrombosis 'or' from prolonged and severe reduction in systemic blood pressure as in shock. |

- Usually limited to the distribution of a single coronary artery and hence unifocal.

- Usually multifocal (may be unifocal)
  - Limited to distribution of a single coronary artery when it results from plaque disruption & thrombosis
  - Usually multifocal as it most often results from reduction in perfusion

(The subendocardial region is the least well perfused region of myocardium and is most vulnerable to any reduction in coronary flow.)

***A transmural infarct*** involves the full thickness of the myocardial wall and is usually caused by acute plaque disruption with superimposed occlusive thrombosis.
***A subendocardial infarct*** is in area of normally diminished perfusion – the inner one-third to one-half of the ventricular wall. These infarcts are typically a result of global atherosclerosis that leads to global borderline perfusion. The critical point is reached by increased oxygen demand, vasospasm, or hypotension without superimposed thrombosis. The myocardial injury is therefore ***multifocal***' - *Unstable Angina and NSTEMI': Journal of emergency medicine.*



**531. Answer is C (Neutrophilic infiltration Surrounding Coagulative necrosis) :** *Robbins 7th ; Hurst 11th / 122*

*The patient in question succumbed to Myocardial infarction after four days of its onset. Charachteristic morphological changes evolve in the heart of patients with MI depend on the duration since the attack.*
***After four days the microscopic examination is most likely to reveal large number of PMNs (Neutrophils) at borders of coagulative necrosis***
**Granulation tissue** *first appears about 6 – 7 days after MI*
**Collagenous tissue** *first appears about 10 days after MI*

**Evolution of MI (Table from 'Hurst')**

| Time of Occlusion | Gross | Histologic |
|---|---|---|
| 12 h | No change / pallor | Wavy fibers |
| 24 – 48 h | Pallor – yellow, soft | Hypereosinophilic fibers, PMNs at borders |
| 3 – 5 days | Yellow center, hyperemic borders | ***Large number of PMNs at border, coagulation necrosis loss of nuclei*** |
| 6 – 10 days | Yellow, depressed central infarct, tanred margins | ***Mummified fibers in center, macrophage phagocytosis + granulation tissue at borders*** |
| 10 – 14 days | Gray red borders, infiltrating central tan-yellow infarct if large | ***Marked granulation tissue, collagen deposition,*** |
| 2 – 8 weeks | Gelatinuous to gray white scar, greater healing at border zone | Collagen deposition with prominent large capillaries. |

**Evolution of MI (Table From Robbins)**

| Time | Gross Features | Light Microscope |
|---|---|---|
| Reversible Injury | | |
| 0 to ½ hr | None | None |
| Irreversible injury | | |
| ½ - 4 hr | None | Usually none; variable waviness of fibres at border |
| 4-12 hr | Occassionally dark mottling | Beginning coagulation necrosis; edema; hemorrhage |
| 12-24 hr | Dark mottling | Ongoing coagulation necrosis; pyknosis of nuclei; myocyte hypereosinophilia; marginal contraction band necrosis; beginning neutrophilic infiltrate |
| 1-3 days | Mottling with yellow-tan infarct center | ***Coagulation necrosis, with loss of nuclei and striations; interstitial infiltrate of neutrophils*** |
| 3-7 days | Hypermic border; central yellow-tan softening | Beginnig disintegration of dead myofibers, with dying neutrophils; early phagocytosis of dead cells by macrophages at infarct border |
| 7-10 days | Maximally yellow tan and soft, with depressed red-tan margins | Well-developed phagocytosis of dead ells; ***early formation of fibrovascular granulation tissue at margins*** |
| 10-14 days | Red-gray depressed infarct borders | Well-established granulation tissue with new blood vessels and collagen deposition |
| 2-8 wks | Gray-white scar, progressive from border toward core of infarct | Increased collagen deposition, with decreased cellularity |
| > 2 mo | Scarring complete | Dense collagen scar |

**532. Answer is B (Necrotic myofibres with presence of neutrophils):** *Robbins 6th/558*

*The patient in question succumbed to myocardial infarction after about 24 hours of the attack. Characteristic morphological changes evolve in the heart of patients with MI depending on duration since the attack.*

***After twenty four hours of the attack light microscope shows coagulative necrosis of myofibrils with loss of nuclei and striations along with an interstitial infiltrate of neutrophils.***

Evolution of morphologic changes in myocardial infarction

| Time | Gross Features | Light Microscope | Electron Microscope |
|---|---|---|---|
| Reversible Injury | | | |
| 0 to ½ hr | None | None | Relaxation of myofibrils; glycogen loss; mitochondrial swelling |
| Irreversible injury | | | |
| ½ - 4 hr | None | Usually none; variable waviness of fibres at border | Sarcolemmal disruption; mitochondrial amorphous densities |
| 4-12 hr | Occassionally dark mottling | Beginning coagulation necrosis; edema; hemorrhage | |
| 12-24 hr | Dark mottling | Ongoing coagulation necrosis; pyknosis of nuclei; myocyte hypereosinophilia; marginal contraction band necrosis; beginning neutrophilic infiltrate | |
| 1-3 days | Mottling with yellow-tan infarct center | ***Coagulation necrosis, with loss of nuclei and striations; interstitial infiltrate of neutrophils*** | |
| 3-7 days | Hypermic border; central yellow-tan softening | Beginnig disintegration of dead myofibers, with dying neutrophils; early phagocytosis of dead cells by macrophages at infarct border | |
| 7-10 days | Maximally yellow tan and soft, with depressed red-tan margins | Well-developed phagocytosis of dead ells; ***early formation of fibrovascular granulation tissue at margins*** | |
| 10-14 days | Red-gray depressed infarct borders | Well-established granulation tissue with new blood vessels and collagen deposition | |
| 2-8 wks | Gray-white scar, progressive from border toward core of infarct | Increased collagen deposition, with decreased cellularity | |
| > 2 mo | Scarring complete | Dense collagen scar | |

**533. Answer is C (1 week old):** *Chandrasoma Taylor 3ed/364: Refer previous question*

*Early formationof granulation tissue is seen about 7-10 days after myocardial infarction.*

**534. Answer is C (Atherosclerosis) :** *Harrison 14th/1394*

*'The most common pathologic condition associated with aortic aneurysm is Atherosclerosis': H14th/1394*

**535. Answer is A (Atherosclerosis) :** *Robbins 6th / 525, 526*

*Atherosclerosis is the major etiological factor in abdominal aortic aneurysm – Robbins*

**Remember:**

- *Atherosclerotic aneurysms most frequently occur in the Abdominal aorta.*[Q]
- *Most common site of abdominal aortic aneurysm is above the bifurcation of aorta and below the renal arteries.*[Q]
- *Most common age group for abdominal aortic aneurysm depends is elderly (> 50 years).* [Q]
- *Risk*[Q] *of rupture of an abdominal aortic aneurysm depends upon its size*[Q] *(aneurysm larger than 5 cm are classified as dangerous*[Q]*)*
- Most common source of infection in a Mycotic abdominal aortic aneurysm is Bacteremia [Q] from a p*rimary Salmonella gastro-enteritis.*[Q]
  (Mycotic aneurysm are abdominal aortic aneurysm that have become infected by lodgment of circulating organisms in the wall)

**536. Answer is A (Ascending Aorta) :** *Robbins 6th/141*

*Aortic aneurysms in Marfan's syndrome occur most frequently in the ascending aorta.*

**Cardiovascular lesions in Marfan's syndrome**

Cardiovascular lesions are the most life threatening features of Marfan's syndrome.

**The two most important lesions are**

| *Mitral valve prolapse*[Q] *(MVP)* | *Dilatation of Ascending Aorta*[Q] |
|---|---|
| • Loss of connective tissue support in mitral valves leaflets makes them soft and blowy creating the so-called *'floppy valve'*.<br>• Mitral regurgitation frequently results. | • Media undergoes cystic necrosis (cystic medionecrosis).<br>• Loss of medial support results in progressive dilatation of aortic valve ring and root of aorta<br>*Severe aortic incompetence*[Q] — *Aortic dissection*[Q] |

**537. Answer is B (Sinus tachycardia):** *Read text below*

*AV fistulas cause short circuiting of blood from an artery to a vein thereby increasing the pulse rate (sinus tachycardia) & cardiac output.*

***Sinus tachycardia*** **:**
It is a regular rhythm with SA node discharging in excess of 100 times/ minute (usually 100-160/min)

Common causes include:

| Physiological | Pathological |
|---|---|
| • High altitude | • Thyrotoxicosis |
| • Exercise | • Anxiety states |
| • Excitement | • Fever and infections |
| • Pregnancy | • Cardiac failure |
| • Pain | • Pulmonary embolism |
| | • AV fistulae. |

**538. Answer is B (↑cardiac output, ↓ total P.R.) :** *Harrison 16th/1608; 14th / 778, 15th/226-27*

*Septic shock is characterized by normal or increased cardiac output and decreased systemic vascular resistance.*

***Septic Shock*** **:** Usually results from a severe decrease in systemic vascular resistance, besides various other features. *Cardiac output is initially normal or even elevated.*

**Infact,** *normal or increased cardiac output and decreased systemic vascular resistance characterize septic shock* (as in Gram negative septicemia here) and distinguish it from cardiogenic, extra-cardiac, obstructive and hypovolumic shock.

**539. Answer is D (Norepinephrine)** : *Harrisons 16th / 1605, 1611; Harrisons 14th / 221, 222 (Detailed in H14th)*

*The patient in question is presenting with features of septic shock. Dopamine is the initial recommended vasopressor agent to maintain blood pressure but is not provided amongst the options. Patients who remain hypotensive despite dopamine should be adminstered norepinephrine and hence norepinephrine is the single best answer of choice here.*

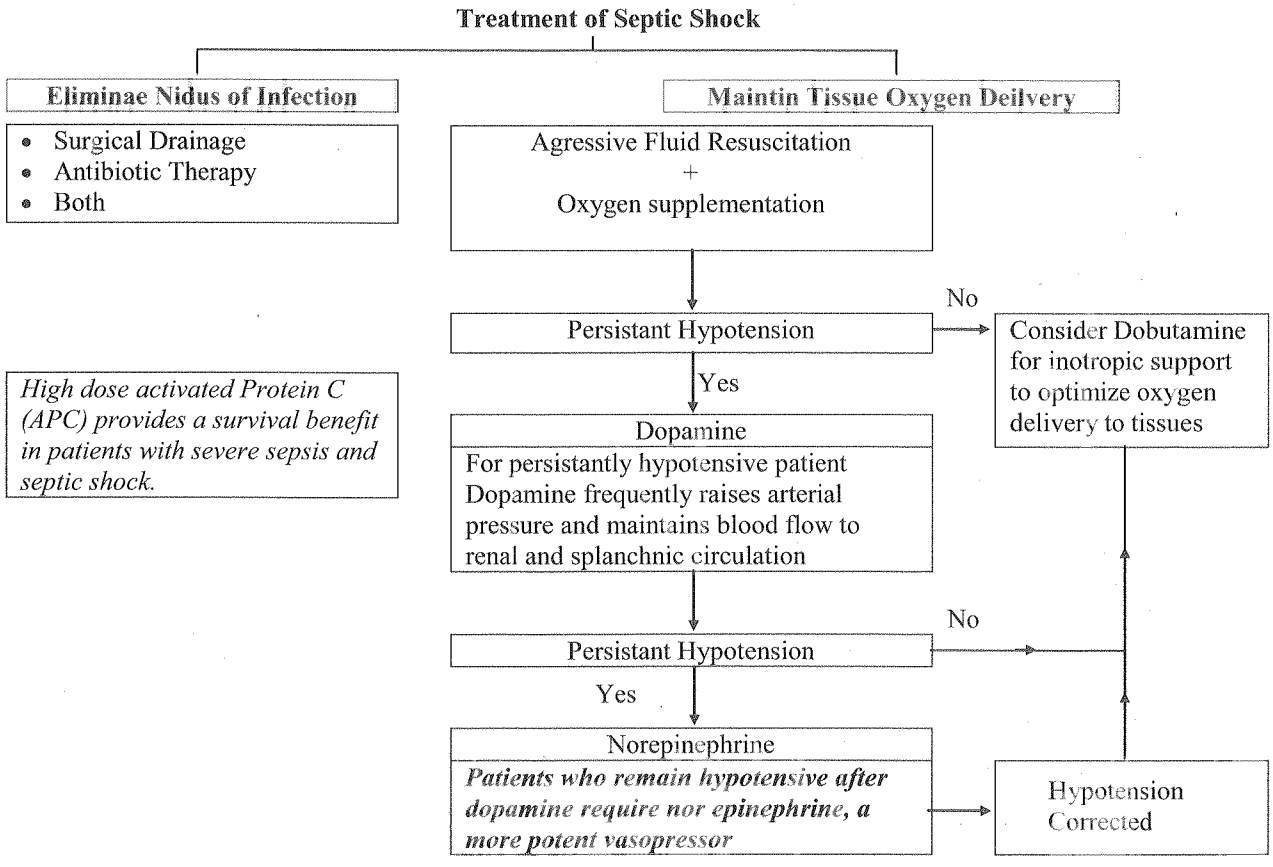
**Harrison 14th / 221 Treatment of septic shock**

*If fluid therapy alone fails to restore adequate arterial pressure and organ perfusion , therapy with vaso pressor agent should be intitiated. For the persistantly hypotensive patient dopamine frequently raises arterial pressure and maintains or enhances blood flow to the renal and splanchnic circulation.* ***Patients who remain hypotensive despite dopamine require nor epinephrine, a more potent vasopressor.***

*Once hypotension, has been corrected to optimize oxygen delivery to tissues, raising a low cardiac index with dobutamine can be useful - Harrisons 14th / 221, 222*

**Harrisons 16th / 605 : Treatment of septic shock**

*In the presence of sepsis, augmentation of cardiac output may require inotropic support with dopamine, nore pinephrine or vaso pressin in the presence of hypotension or with dobutamine if arterial pressure is normal*




**540. Answer is A (Acute Tubular necrosis):** Harrison 18th/p 2227 *Harrisons 17th/1699*

*Most common cause of renal failure in patients with septic shock is Acute tubular necrosis*

*Most renal failure is due to acute tubular necrosis induced by hypotension or capillary injury although some patients also have glomerulonephritis, renal cortical necrosis or interstitial nephritis-Harrison's 17th/1699*

**541. Answer is B (Associated with pulmonary vasoconstriction) :** Harrison 18th/p 280 *Harrison 16th / 205; 17th/ 224*

*Although the mechanism of high altitude pulmonary edema remains obscure most studies suggest pulmonary vasoconstriction (venconstriction or arteriolar constriction) as the prime mechanism.*

**HAPE : High Altitude Pulmonary Edema**

This is a serious complication usually occruing at exposure to high altitude (>300m) in association with severe physical exercise and is classically seen in unacclametized healthy individuals.

**Pulmonary vasoconstriction has been suggested as the prime mechanism.**
*"Studies have been conflicting, some suggesting pulmonary venous constriction and other indicating pulmonary arteriolar constriction as the prime mechanism."- Harrison*

**May occur in both acclamatized and unacclamatized individuals**
"*Well recognized in unacclamatized yet otherwise healthy persons.*"
"***Acclamatized high altitude natives also develop this syndrome*** upon return to high altitude after a relatively brief sojourn at low altitudes." - *Harrison*

**HAPE is exacerbated by exercise and is associated with high cardiac output.**
*Increased cardiac output* and pulmonary arterial pressures with exercise combined with hypoxic pulmonary arteriolar constriction which is more prominent in young persons may combine to make this an example of prearteriolar high pressure pulmonary edema.

**542. Answer is D (Mid diastole):** *Harrison's Advances in Cardiology 'by Braunwald (2002/227); 'Multislice CT' by Becker 3rd/ 197; MD CT: A Practical Approach (2006) / 213; MD CT: From Protocols to Practice (2008) / 213; Computed Tomography of the Cardiovascular System (2007) / 110*

***Mid Diastolic phase of the cardiac cycle is associated with the lowest mean motion of the heart***

*'Imaging for electron beam tomography (EBT) is performed during mid- diastole when the heart motion is at minimum'*
*- Harrison's Advances in Cardiology (2002) / 227*

*'The period in which heart has the least motion is usually (but not always) in mid- diastole'*
*- 'MDCT: A practical approach by Saini, Rubin & Kalra (2006) /* 213

**Minimum Cardiac Motion and its Application**

- Early detection of coronary artery disease is possible with the use of Computed Tomography (CT) and Magnetic Resonance Imaging (MRI)
- The application of these tools to cardiac imaging is however severely limited by motion artifacts as the heart is constantly in motion completing an entire cycle of contraction and relaxation in about 1 second.
- *Application of these tools to cardiac imaging requires a 'Window' where cardiac motion is minimum to reduce motion artifacts and achieve meaningful images.*
- The optimal trigger point for such imaging is the phase of the cardiac cycle when cardiac motion is minimum. This period where cardiac motion is minimum is usually (but not always) the mid diastolic phase of cardiac cycle, just before atrial systole.

| |
|---|
| *Diastole consists of four distinct phase: isometric relaxation, early rapid filling, diastasis and atrial systole. Of these four phases diastasis has the least mean cardiac motion.* |

- The phase of minimum cardiac motion is however variable and depends on several factors especially the heart rate

| |
|---|
| *Mid –diastole represents the phase of minimum cardiac motion only in patients with low / intermediate heart rates* |

*As heart rate increases the duration of diastole is shortened and the minimum mid- diastolic motion increases. In contrast the duration of systole is less affected by changes in heart rate. The late systolic phase provides another window where cardiac motion is low and at high heart rates the lowest motion may be recorded in late systole rather than during mid – diastole.*

| *Note* |
|---|
| *Optimum phase for imaging coronary vessels (minimum cardiac motion) at low/intermediate heart rates is Mid- diastolic phase* |
| *Optimum phase for imaging coronary vessels (minimum cardiac motion) at high rates is variable and may occur in late systole.* |

- This phase of minimum cardiac motion also varies on whether the Left Atrium. Right Atrium, Left Ventricle and Right Ventricle are being specifically imaged.

| Phases of Relatively Rapid Cardiac motion | Phase of Relatively minimal cardiac motion |
|---|---|
| • Early systole | • ***Mid diastole (diastasis)*** |
| • Mid systole | • *Early diastole (During Isovolumetric relaxation)* |
| • Early diastole (during rapid filling) | • *Late systole* |
| • Late diastole (Atrial systole) | |

**543. Answer is D (Aortic Aneurysm):** *Harrison's 17th/1172, Hurst's 12th/2119; Braunwald' 8th/1794, 1795*

***Aortic Aneurysm has not been mentioned as a complication of HIV infection***
*Although accelerated atherosclerosis and vasculitis have been mentioned as complications of HIV infection, an increased incidence of Aortic Aneurysm has not been listed as a complication in any standard textbook.*
***Aortic aneurysm is thus the most unlikely complication amongst the options provided and the single best answer of exclusion***

**Pericardial effusion and cardiac tamponade may be seen in HIV infection**

*'HIV infection should be suspected whenever young patients present wth pericardial effusion or tamponade'*
*– Braunwald's 8th/1798*

*Asymptomatic Pericardial Effusion* is common in HIV patients and occurs in about 11% of AIDS patients (*Braunwald*)
*Pericardial Tamponade* is an uncommon / rare manifestation in HIV patients but may be seen (*Harrison / Braunwald*)

**Cardiomyopathy may be seen in HIV infection**

*Dilated cardiomyopathy associated with congestive heart failure (HIV cardiomyopathy) is the most common clinically significant cardiac finding as a primary consequence to HIV infection (Harrison's)*

| Cardiac Manifestation of HIV/AIDS | |
|---|---|
| ***Pericardial Effusion*** *(Rarely **pericardial tamponade**)* | • Idiopathic<br>• Infectious (viral, bacterial especially tuberculous, and fungal)<br>• Neoplastic (Kaposi sarcoma and non-Hodgkin lymphoma) |
| *Heart muscle disease* | • Myocarditis (idiopathic/lymphocytic, specific infections, toxins)<br>• Dilated ***cardiomyopathy*** & LV dysfunction |
| *Endocarditis* | • Marantic (non bacterial thrombotic endocarditis)<br>• Infective |
| *Tumors* | • Kaposi sarcoma<br>• Lymphoma |
| *Right ventricular dysfunction & Pulmonary hypertension* | • Primary<br>• Secondary (recurrent chest infections, thromboembolism) |
| *Premature atherosclerosis & coronary artery disease* | |
| *Adverse drug effects* | • Hyperlipidemia<br>• Proarrhythmia |
| *Vasculitis and Lipodystrophy* | • Drug Therapy : Protease inhibitors |
| *Autonomic dysfunction* | • Drug therapy, CNS disease Prolonged immunodeficiency, malnutrition |

**544. Answer is A (Hypertension):** *Multiple references*

*The most common cause of Left Ventricular Hypertrophy is Systemic Hypertension*
***Left Ventricular Hypertrophy may be produced as a result of all of the above conditions but systemic hypertension remains the single most common cause.***

| Left Ventricular Hypertrophy (LVH) |
|---|
| **Pressure overload states:**<br>• Hypertension (most common cause of LVH).<br>• Aortic stenosis<br>• Coarctation of Aorta<br>**Volume overload states:**<br>• Aortic or mitral regurgitation<br>**Hypertrophic cardiomyopathy (HCM):**<br>• A group of genetic diseases of the cardiac sarcomere characterized by hypertrophy of the left ventricle. |

Q ***The most common cause of Left Axis Deviation of ECG is Left Anterior Hemiblock***

**545. Answer is C (MRI):** *Harrison 18th/ 1963; The Cleveland Clinic Cardiology Board Review Series 2nd/141; Oxford Textbook of Heart Failure (Oxford University Press) 2011/ 85*

*Cardiac MRI is the investigation of choice in Cardiomyopathy from Hemochromatosis.*

*Cardiac MRI helps distinguish amongst various causes of restrictive cardiomyopathy. Cardiac MRI in hemochromatosis allows non-invasive detection and quantification of myocardial iron load and distribution. Cardiac MRI is the imaging modality of choice as Echocardiography may be unable to distinguish hemochromatosis from dilated cardiomyopathy*

**546. Answer is A (Mitral Valve Prolapse):** *Valvular Heart Disease: A Companion to Braunwald's Heart Disease by Otto (Elsevier Health Sciences), 2009/ 403; Mayo Clinic Internal Medicine Review 7th/ 358*

*The single most common cardiovascular abnormality seen in patients with Marfan's Syndrome at the time of presentation is Mitral Valve Prolapse.*

***Mitral Valve Prolapse is the most frequent abnormality seen at the time of presentation (80 – 100%)***
*-Valvular Heart Disease: A Companion to Braunwald's Heart Disease*

***Mitral Valve Prolapse and Dilation of the Ascending Aorta at the level of aortic sinuses are the two most common cardiovascular abnormalities seen in patients with Marfan's Syndrome***

- *Mitral Valve Prolapse is the single most common cardiovascular abnormality*
- *Dilation of the Ascending Aorta at the level of aortic sinuses is the next most common anomaly.*

**547. Answer is A (Vascular Access Site Bleeding):** *Braunwald's 9th/Chapter 20; Blueprints Cardiology 2nd/33; Textbook of Cardiovascular Intervention (Springer), 2013/76*

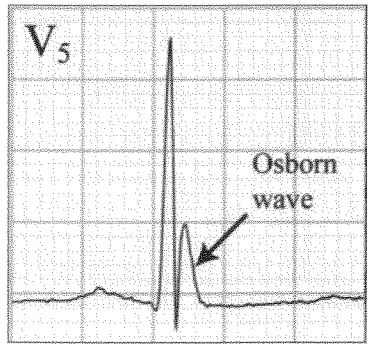
***The most common complication of cardiac catheterization is bleeding from the vascular access site. This may be seen either early or late after catheterization and may manifest as overt bleeding or as a hematoma.***

**548. Answer is B (Hypothermia):** *The Washington Manual Cardiology Subspecialty Consult (2008)/235*

***Osborne waves also called J waves are typically seen in Hypothermia.***

**J Wave; Osborne Wave** *(Camel-hump sign, Late delta wave, Hat-hook junction, or Current of injury)*

- ***J wave (Also termed the' Osborne wave) is the most common ECG finding in patients with hypothermia***
- *It is characterized as a positive deflection in the terminal portion of the QRS complex and elevation of the J point*
- *J waves are most commonly found in the anterior and lateral precordial leads and in lead II, although they may be present in only a single lead*
- *They usually occur in patients with core body temperatures less than 32° C (90°F) and often appear larger when the temperature is below 30°C (86°f).*
- *The size of the J waves usually correlates inversely with the body temperature; as the body temperature increases, the J wave gradually becomes smaller.*




**549. Answer is D (Arrhythmogenic right ventricular dysplasia):** *Harrison 18th/1896*

***Epsilon wave also called "post excitation wave" is typical of Arrhythmogenic right ventricular dysplasia.***

Arrhythmogenic right ventricular dysplasia (ARVD, also known as arrhythmogenic right ventricular cardiomyopathy – ARVC) is a non-ischemic cardiomyopathy characterised by fibrofatty degeneration of the right ventricle resulting in recurrent ventricular arrhythmias originating from the right ventricle (right ventricular tachycardia). Epsilon wave also called "post excitation wave" akin to the prexcitation delta wave seen in WPW syndrome is found in about 50% of patients with ARVD. This is described as a terminal notch in the QRS complex and is believed to be due to slowed intra-ventricular conduction.

Triangle of Dysplasia

The origin of the ectopic beats is usually from one of the three regions of fatty degeneration often referred as the 'triangle of dysplasia'. This includes :

- The RV outflow tract,
- The RV inflow tract, and
- The RV apex.

**550. Answer is D (Hypertension):** *Mayo Clinic Cardiology: Concise Textbook 4th/ 592*

***Hypertension is the single most important, modifiable risk factor for stroke.***
*Treatment of hypertension to desired Blood Pressure is the most cost effective strategy for the prevention of both ischemic and haemorrhagic stroke.*

- *Cigarette smoking is the single most important modifiable risk factor for atherosclerosis*
- *Smoking is the single most important modifiable risk factor for the development of Peripheral Artery Disease (PAD)*
- *Smoking cessation is the single most important target for coronary artery disease (CAD) Prevention*

**551. Answer is D (Evaluation of Left Atrial Appendage Thrombi):** *Harrison 18th/ 1843; Principles of Echocardiography: Expert Consult by Stuart J. Hutchison (Saunders-Elsevier) / 327*

***Trans-esophageal echocardiogram (TEE) is preferred to Trans-thoracic echocardiogram (TTE) for smaller, atrial and posterior masses such as the Left Atrial Appendage Thrombi.*** *TTE is the standard test for the noninvasive evaluation of pericardial disease. Identification of vegetations on tricuspid valves is no better overall by TEE than by TEE (as the tricuspid valve is equidistant from the chest wall and the esophagus). Very anterior masses, Such as left ventricular apical thrombi, are equally well and far more easily imaged by TTE.*

**Trans-esophageal echocardiogram (TEE) vs. Trans-thoracic echocardiogram (TTE)**

Trans-esophageal Echocardiography (TEE) is generally more sensitive than Trans-thoracic Echocardiography (TTE) and provides a unique window for high resolution imaging of posterior structures of the heart particularly the left atrium, mitral valve and aorta. TEE is however an invasive and more expensive procedure and hence its indications must be weighed against these factors and TTE remains the initial investigation of choice for most situations. However if a high clinical index of suspicion remains after a negative or non-diagnostic transthoracic study, Trans-esophageal echocardiography should be considered.

Situations in which Trans-esophageal echocardiography should be performed as the initial test of choice include

(1) Those patients in whom image quality on chest wall imaging is unacceptable.

(2) Those with prosthetic valves, and

(3) Those in whom complications such as abscess formation are suspected on clinical grounds.

- TEE is not superior to TTE for the detection of large masses, or anterior masses, both of which are generally well imaged by TTE.

| The incremental yield of TEE is achieved for smaller, atrial and posterior masses such as the following; |
|---|
| • *Left atrial appendage thrombi*<br>• Left atrial thrombi (If small or flat)<br>• Thrombi/tumors of the superior vena cava<br>• Masses attached to the right heart<br>• Masses attached to the descending aorta |

- Large masses, such as most Myxomas, are detected virtually equally well by TTE as by TEE, but are imaged in greater detail by TEE,
- Very anterior masses, Such as ***left ventricular apical thrombi,*** are equally well and far more easily imaged by TTE
- Identification of ***vegetations on tricuspid valves*** is no better overall by TEE than by TEE (as the tricuspid valve is equidistant from the chest wall and the esophagus).
- TTE is the standard test for the noninvasive evaluation of pericardial disease.

**552. Answer is A (Lev's Disease) :** *Textbook of Cardiovascular Medicine by Topol 3rd/1044*

***Progressive idiopathic fibrosis of the proximal bundle branch fibres is termed as LEV Disease.***

| | |
|---|---|
| Lev's Disease | *Progressive idiopathic fibrosis of the proximal bundle branch fibres (usually occurs in relatively older population)* |
| Lenegre's Disease | *Progressive idiopathic fibrosis of the more distal/peripheral portion of the bundle branches (usually occurs in younger population)* |
| Ashman Phenomenon | Transient bundle branch block resulting from an aberrant intraventricular conduction abnormality that occurs in response to a change in QRS cycle length (When a short cycle follows a long one). RBBB aberration is typically more common than LBBB.<br>*Ashman's phenomenon should be suspected in atrial fibrillation when there is a long cycle followed by a short cycle, with the subsequent QRS complex manifesting a right bundle branch block pattern.* |
| Brugada Syndrome | Syncopal episodes and/or sudden death with a characteristic electrocardiogram (ECG) pattern of right bundle branch block and ST segment elevation in leads V1 to V3.<br>*The diagnosis Brugada syndrome is based on the history of sudden death with the typical electrocardiographic pattern of ST segment elevation in leads V1-V3, with or without right bundle branch block. The presence of RBBB is not essential to the diagnosis of Brugada Syndrome. Patients with Brugada Syndrome may have a structurally normal heart.* |

**553. Answer is D (Ashman Phenomenon):** *Clinical Arrhythmology and Electrophysiology: A Companion to Braunwald's Heart Disease 2nd/ 194; Making Sense of the ECG: Cases for Self Assessment by Houghton 2nd/ 138; ECG Interpretation (Lippincott) / 169*

***Ashman Phenomenon is more commonly associated with an RBBB aberration than LBBB.*** *Ashman's phenomenon should be suspected in atrial fibrillation when there is a long cycle followed by a short cycle, with the subsequent QRS complex* ***manifesting a right bundle branch block pattern.***

**Ashman Phenomenon is more commonly associated with an RBBB aberration than LBBB**

*Ashman's phenomenon is a transient functional bundle branch block resulting from an aberrant intraventricular conduction abnormality that occurs in response to a change in QRS cycle length (When a short cycle follows a long one). RBBB aberration is typically more common than LBBB. Ashman's phenomenon should be suspected in atrial fibrillation when there is a long cycle followed by a short cycle, with the subsequent QRS complex manifesting a right bundle branch block pattern.*

**Acute Myocardial Infarction, Aortic Valve disease and Lev Disease are all associated with LBBB**

| Selected Causes of Left Bundle Branch Block |
|---|
| • *Coronary Heart Disease/ Acute MI (frequently with impaired left ventricular function)* |
| • *Hypertensive Heart Disease* |
| • *Aortic Valve Disease* |
| • *Cardiomyopathy* |
| • *Idiopathic fibrosis of the bundle branch fibres (Lev disease and Lenegre Disease)* |

**554. Answer is D (Right Bundle Branch Block):** *Harrison 18th/ 1898, 1899; Clinical Arrhythmology and Electrophysiology: A Companion to Braunwald's Heart Disease 2nd/ 662*

***Brugada Syndrome is typically associated with a Right Bundle Branch Block (RBBB) pattern on EKG.***

**Brugada Syndrome** is characterized by syncopal episodes and/or sudden death and a characteristic electrocardiogram (ECG) with a pattern of ***Right Bundle Branch Block with an ST segment elevation in leads V1 to V3***. The diagnosis Brugada syndrome is based on the history of sudden death with the typical electrocardiographic pattern of ST segment elevation in leads V1-V3, with or without right bundle branch block. *The presence of RBBB is not essential to the diagnosis of Brugada Syndrome.* Patients with Brugada Syndrome may have a structurally normal heart.

***

# Respiratory System

## ESSENTIAL REVISION NOTES

### Respiratory failure

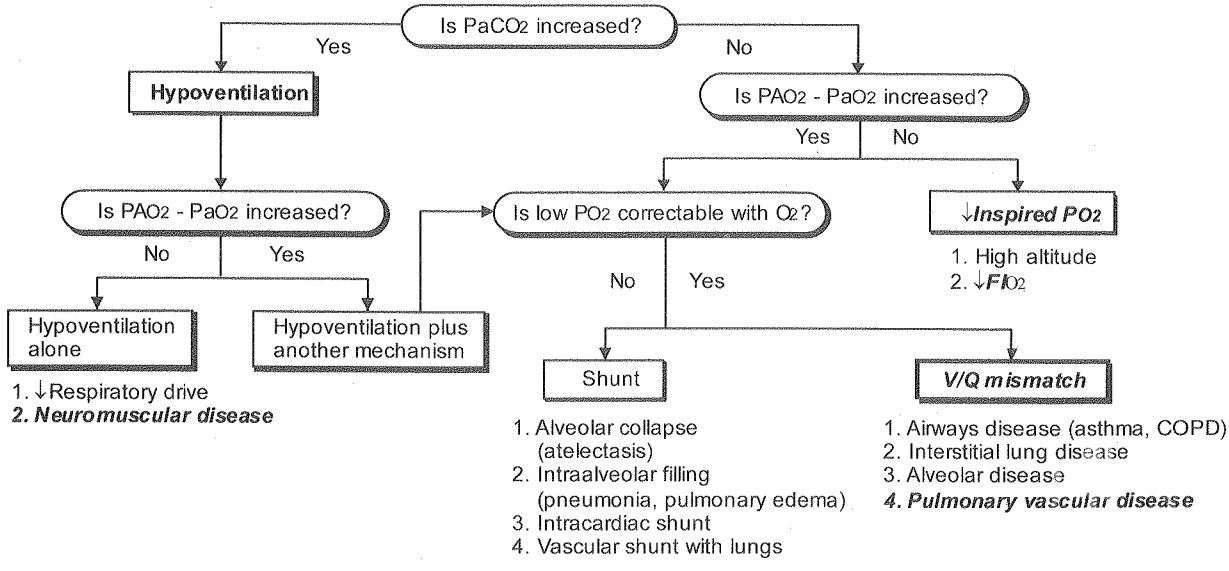
***Respiratory failure*** *is defined as a disorder wherein, lung function is inadequate to meet the metabolic demands of the individual and is unable to maintain normal arterial gas levels in the blood.*

**It is of two types:**

| Type I Respiratory failure | Type II Respiratory failure |
|---|---|
| Represents failure of oxygenation and is characterized by a low $PaO_2$ with normal or low $PaCO_2$.<br>$PaO_2$ : Low (< 60 mm Hg)<br>$PaCO_2$ : Normal or low (≤ 49 mm Hg)<br>$P_{A-a}O_2$ : Increased | Represents a defect in ventilation (hypoventilation) and is characterized by decreased $PaO_2$ with increase $PaCO_2$.<br>$PaO_2$ : Decreased (< 60 mm Hg)<br>$PaCO_2$ : Increased (> 49 mm Hg)<br>$P_{A-a}O_2$ : Normal |
| **Causes :** | **Causes :** |
| This type is caused by conditions which affect oxygenation, like:<br>• Parenchymal diseases (V-Q mismatch)<br>• Diseases of vasculature/shunts<br>Examples:<br>- *Pneumonia* Q<br>- *ARDS* Q<br>- *Emphysema* Q<br>- *Right to left shunts* Q | This type is caused by conditions causing hypoventilation as in:<br>• Obstructive lung disease:<br>*COPD, F. body*<br>• Decreased central respiratory drive<br>*e.g. CNS disorders like : Brain injury, Meningitis*<br>• Weakness of respiratory muscle e.g.<br>- *Peripheral N.S. disorders like: M. gravis.*<br>- *Interstitial lung disease.* Q<br>- *MS disorders like polymyositis.*<br>- *Rib cage disorders : Kyphoscoliosis.* |

| Type I Respiratory failure | Type II Respiratory failure |
|---|---|
| *Hypoxemia with decreased $PaCO_2$* | *Hypoxemia with increased $PaCO_2$* |

### Approach to patient with Hypoxia (Hypoxemia)



# Obstructive versus Restrictive Respiratory Diseases

## Classification of Respiratory Disorders

**Respiratory disease**

**Obstructive**

1. ***Asthma*** [Q]
2. ***COPD – Chronic bronchitis*** [Q] **–** ***Emphysema*** [Q]
3. ***Bronchiectasis*** [Q]
4. ***Cystic fibrosis***
5. ***Bronchiolitis***

**Restrictive**

**Parenchymal**

- *Sarcoidosis* [Q]
- *Pneumoconiosis* [Q]
- *Idiopathic pulmonary fibrosis* [Q]
- *Drug/ Radiation* [Q] induced interstitial lung disease

**Extra Parenchymal**

1. Neuromuscular diseases
   - *Diaphragmatic palsy* [Q]
   - GB syndrome
   - Muscular dystrophy
   - Cervical spine injury
2. Chest wall
   - *Kyphoscoliosis* [Q]
   - Obesity
   - Ankylosing spondylitis

***The hallmark in obstructive pattern of disease is a decrease in expiratory flow rates. Decrease in Forced Expiratory flow rate ($FEF_{25-75}$) and $FEV_1/FVC$ are characteristic.***

## Differences between Obstructive and Restrictive Respiratory Diseases

| PFT Result | Obstructive Pattern | Restrictive Pattern |
|---|---|---|
| *$FEV_1$* | *Decreased (<80% predicted) (Decreased out of proportion to FVC)* | *Decreased (May be preserved) (Decreased in proportion to FVC)* |
| *FVC* | *Decreased (May be preserved)* | *Decreased (<80% predicted)* |
| *$FEV_1/FVC$ ($FEV_1$%)* | *Decreased (<0.7)* | *Normal or Increased (>0.7)* |
| *$FEF_{25-75}$* | *<50% predicted* | *Decreased in proportion to loss of lung volume* |
| *TLC* | *Normal or elevated* | *Decreased* |
| *DLCO* | *Normal*<br>*Decreased in Emphysema* | *Decreased in intrinsic restrictive lung disease.*<br>*Normal in neuromuscular or musculoskeletal restrictive disease* |

***$FEV_1$**=forced expiratory volume in one second; **FVC**=Forced Vital Capacity; **$FEF_{25-75}$**=Forced Expiratory Flow at 25%=75% vital capacity; **TLC**= Total Lung Capacity; **DLCO**=Diffusion Capacity of the Lung for Carbon monoxide.*

## Diffusion capacity of Lung for carbon monoxie (DLCO)

Diffusion capacity is altered in disease affecting the functional integrity of the alveolar capillary membrane.

| Decreased $D_{LCO}$ (Diffusion capacity) | Increased $D_{LCO}$ (Diffusion capacity) |
|---|---|
| 1. **Interstitial lung disease**: scarring of alveolar capillary units diminishes area of alveolar capillary bed as well as pulmonary blood volume<br>2. **Emphysema:** alveolar walls are destroyed so the surface area of alveolar capillary bed is diminished<br>3. **Recurrent pulmonary embolism and Primary pulmonary hypertension:** disease causes a decrease in cross sectional area and volume of pulmonary vasculature | 1. **Alveolar haemorrhage:** as in Good pasture's syndrome: haemoglobin contained in erythrocytes in alveolar lumen binds Co so exhaled carbon monoxide concentration is diminished & $D_{LCO}$ is increased<br>2. **Congestive heart failure:** May be elevated if pulmonary blood volume is increased. Once pulmonary edema ensues $D_{LCO}$ may decrease as and the net $D_{LCO}$ depends on the opposing influences. |

### Three main categories are associated with lowered DLCO

- *Emphysema* [Q]
- *Interstitial Lung Disease* [Q]
- *Pulmonary vascular disease (Recurrent Pulmonary emboli or Primary Pulmonary Hypertension)* [Q]

## Alveolar arterial differeitce in oxygen

Increased $PaO_2 - PaO_2$
(Alveolar arterial difference in oxygen)

| Correctible with oxygen V/Q Mismatch | Not correctible with oxygen Shunt |
|---|---|
| **V/Q Mismatch:**<br>- Airway disease (Asthma, COPD)<br>- Interstitial lung disease<br>- Alveolar disease<br>- Pulmonary vascular disease | **Shunt:**<br>- Alveolar collapse<br>- Intra alveolar filling<br>  - Pneumonia<br>  - Pulm edema<br>- Intracardiac shunt<br>- Vascular shunt within lung |

# Bronchial Asthma

## Features of Asthma: Chronic inflammatory disorder

| Features of Asthma |
|---|
| • ***Chronic inflammatory disorder*** |
| • ***Hyperresponsiveness of airways (AHR)*** |
| • *Airway epithelial shedding* |
| • *Subepithelial fibrosis and thickening of basement membrane* |
| • *Hypertrophy and Hyperplasia of airway smooth muscle* |
| • *Increased mucosal blood flow (vascular congestion)* |
| • *Microvascular leakage resulting in **airway edema** and plasma exudation into airway lumen* |
| • ***Mucus Hypersecretion** and formation of viscid mucus plugs that occlude airways* |
| • *Airway remodelling* |
| • *Defects in autonomic neural control* |

## Charachterisitc microscopically identifiable features described in sputum of Bronchial Asthma Patients

| The microscopically identifiable features described in sputum are three 'C's |
|---|
| ***C**harcot Leyden crystals: Derived from granules of eosnophils and found only in Asthma* |
| ***C**urshmann spirals: Curiously twisted casts of airways : Whorls of shed epethelium* |
| ***C**reola bodies: Clumps of cells or isolated metaplastic cells* |

## Classification of Bronchial Asthma

**Asthma**

| Extrinsic Asthma / Allergic Asthma | Intrinsic Asthma /Idiosyncratic Asthma |
|---|---|
| • History of Atopy is present | • No history of Atopy (Concomitant nasal polyps are usually present and patients may be aspirin sensitive) |
| • Attacks related to environmental exposures | • Attacks not related to environmental exposures: Occur without provocation |
| • IgE antibody levels are ↑ ed | • IgE antibody levels are normal |
| • Early onset of disease (young) | • Delayed onset of disease (Adult onset Asthma) |
| • Usually is less severe, intermittent Asthma that may however progress to severe persistent Asthma | • Usually have more severe persistent Asthma |

## Features of Intrinsic Asthma

| **Features of Intrinsic Asthma**<br>*(Nonatopic asthma- Approximately 10% of asthmatic patients are intrinsic )* |
|---|
| • ***Negative Family History of allergy*** |
| • ***Negative skin test to common inhalant allergens (Not primarily caused by allergy)*** |
| • *Normal serum concentration of IgE.* |
| • *Concomitant nasal polyps (Common)* |
| • *Sensitivity to aspirin and related chemicals* |
| • *Later onset of disease (adult-onset asthma)* |
| • *More servere, persistent disease/asthma.* |

## Classification of severity of asthma exacerbations

| | Mild | Moderate | Severe | Impending Respiratory Failure |
|---|---|---|---|---|
| ***Symptoms*** | | | | |
| Breathlessness | With activity | With talking | At rest | At rest |
| Speech | Sentences | Phrases | Words | Mute |
| ***Signs*** | | | | |
| Body position | Able to recline | Prefers sitting | Unable to recline | Unable to recline |
| Respiratory rate | Increased | Increased | Often > 30/min | > 30/min |
| Use of accessory respiratory muscle | Usually not | Commonly | Usually | Paradoxical thoracoabdominal movement |
| ***Breath sounds*** | ***Moderate wheezing at mid-to-end-expiration*** | ***Loud wheezes throughout expiration*** | ***Loud inspiratory and expiratory wheezes*** | ***Little air movement without wheezes (silent chest)*** |
| ***Hear rate (beats/min)*** | <100 | 100-120 | ***>120*** | Relative bradycardia |
| ***Pulsus paradoxus*** (mm Hg) | < 10 | 10-25 | ***Often > 25*** | Often absent |
| Mental status | May be agitated | Usually agitated | Usually agitated | Confused or drowsy |
| Functional assessment | | | | |
| ***PEF (% predicted )*** | > 80 | 50-80 | ***< 50*** | < 50 |
| $Sao_2$ (%, room air) | > 95 | 91-95 | < 91 | < 91 |
| $Pao_2$ (mm Hg, room air) | Normal | > 60 | < 60 | <60 |
| $Paco_2$ (mm Hg) | < 42 | < 42 | ≥ 42 ***(Respiratory acidosis)*** | ≥ 42 |

## Classification of Asthma Severity (Intermittent vs. Persistent) Based on Different Age Groups

| Components of SEVERITY | | Age (Years) | Classification of Asthma SEVERITY (Intermittent vs. Persistent) | | | |
|---|---|---|---|---|---|---|
| | | | Intermittent | Persistent | | |
| | | | | Mild | Moderate | Severe |
| Impairment | Symptoms | All | ≤ 2 days/week | > 2 days/week but not daily | Daily | Throughout the day |
| | Nighttime awakenings | 0 – 4 | 0 | 1–2x/month | 3–4x/month | > 1x/week |
| | | ≥ 5 | ≤ 2x/month | 3–4x/month | > 1x/week but not nightly | Often 7x/week |
| | SABA use for symptom control | All | ≤ 2 days/week | > 2 days/week but not daily | Daily | Several times a day |
| | Interference with normal activity | All | None | Minor limitation | Some limitation | Extremely limited |
| | Lung function: | | | | | |
| | $FEV_1$ (predicted) or PEF (personal best) | ≥ 5 | Normal $FEV_1$ between exacerbations > 80% | > 80% | 60–80% | < 60% |
| | $FEV_1/FVC$ | 5 – 11 | > 85% | > 80% | 75–80% | < 60% |
| | | ≥ 12 | Normal | Normal | Reduced 5% | Reduced > 5% |
| Risk | Exacerbations requiring oral corticosteroids | 0 – 4 | ≤ 1x/year | ≥ 2x in 6 months or ≥ 4 wheezing episodes/year lasting > 1 day AND risk factors for persistent asthma | | |
| | | 5 – 11 | | ≥ 2x/year | | |
| | | ≥ 12 | | Consider severity and interval since last exacerbation. Frequency and severity may fluctuate over time for patients in any severity category. Relative annual risk of exacerbations may be related to $FEV_1$. | | |
| Recommended step for starting treatment | | 0 – 4 | Step 1 | Step 2 | Step 3 | Step 3 |
| | | 5 – 11 | | | | Step 3 or 4 |
| | | ≥ 12 | | | | Step 4 or 5 |
| | | All | | | | Consider short course of oral corticosteroids |
| | | All | In 2–6 weeks, evaluate level of asthma control that is achieve and adjust therapy accordingly. For children 0–4 years old, if no clear benefit is observed in 4–6 weeks, stop treatment and consider alternative diagnosis or adjusting therapy. | | | |

$FEV_1$, forced expiratory volume in 1 second; FVC, forced vital capacity; PEF, peak expiratory flow; SABA, short-acting $beta_2$-agonist

*Note:*

*Asthma severity is the intrinsic intensity of the disease process and dictates which step to initiate treatment.*

*The classification of severity or level is based on the most severe impairment or risk category in which any feature occurs*

# Stepwise Approach for Managing Asthma Long Term

Step UP if needed (first check inhaler technique, adherence, environmental control, and comorbid conditions)
ASSESS CONTROL
Step DOWN if possible (and asthma is well controlled for at least 3 months)

| | | Step 1 | Step 2 | Step 3 | Step 4 | Step 5 | Step 6 |
|---|---|---|---|---|---|---|---|
| 0 – 4 Years | | Intermittent Asthma | Persistent Asthma: Daily Medication<br>Consult with asthma specialist if step 3 care or higher is required. Consider consultation at step 2. | | | | |
| | Preferred | SABA as needed | Low-dose ICS | Medium-dose ICS | Medium-dose ICS<br>+<br>LABA *or* montelukast | High-dose ICS<br>+<br>LABA *or* montelukast | High-dose ICS<br>+<br>Oral corticosteroids<br>+<br>LABA *or* montelukast |
| | Alternative | | Cromolyn *or* montelukast | | | | |
| | | Patient education and environmental control at each step. | | | | | |
| | Rescue Medication | • SABA as needed for symptoms. Treatment intensity depends on symptom severity.<br>• With viral respiratory symptoms, SABA every 4–6 hours up to 24 hours (longer with physician consult).<br>• Consider short course of oral corticosteroids if exacerbation is severe or if patient has history of previous severe exacerbations.<br>• Frequent or increasing use of SABA may indicate inadequate control and the need to step up treatment. | | | | | |
| 5 – 11 Years | | Intermittent Asthma | Persistent Asthma: Daily Medication<br>Consult with asthma specialist if step 4 care or higher is required. Consider consultation at step 3. | | | | |
| | Preferred | SABA as needed | Low-dose ICS | Low-dose ICS<br>+<br>LABA, LTRA, *or* Theophylline<br>*OR*<br>Medium-dose ICS | Medium-dose ICS<br>+<br>LABA | High-dose ICS<br>+<br>LABA | High-dose ICS<br>+<br>LABA<br>+<br>Oral corticosteroids |
| | Alternative | | Cromolyn, LTRA, Nedrocromil, *or* Theophylline | | Medium-dose ICS<br>+<br>LTRA *or* Theophylline | High-dose ICS<br>+<br>LTRA *or* Theophylline | High-dose ICS<br>+<br>LTRA *or* Theophylline<br>+<br>Oral corticosteroids |
| | | Patient education and environmental control, and management of comorbidities at each step.<br>Step 2-4: Consider subcutaneous allergen immunotherapy for patients who have allergic asthma. | | | | | |
| | Rescue Medication | • SABA as needed for symptoms – up to 3 treatments at 20-minute intervals initially. Treatment intensity depends on symptom severity.<br>• Consider short course of oral corticosteroids.<br>• Increasing use of SABA or use > 2 days/week for symptom relief (not prevention of EIB) generally indicates inadequate control and the need to step up treatment. | | | | | |
| ≥ 12 Years | | Intermittent Asthma | Persistent Asthma: Daily Medication<br>Consult with asthma specialist if step 4 care or higher is required. Consider consultation at step 3. | | | | |
| | Preferred | SABA as needed | Low-dose ICS | Low-dose ICS<br>+<br>LABA<br>*OR*<br>Medium-dose ICS | Medium-dose ICS<br>+<br>LABA | High-dose ICS<br>+<br>LABA | High-dose ICS<br>+<br>LABA<br>+<br>Oral corticosteroid |
| | Alternative | | Cromolyn, LTRA, Nedrocromil, *or* Theophylline | Low-dose ICS<br>+<br>LTRA, Theophylline, *or* Zileuton | Medium-dose ICS<br>+<br>LTRA, Theophylline, *or* Zileuton | Consider Omalizumab for patients who have allergic asthma | Consider Omalizumab for patients who have allergic asthma |
| | | Patient education and environmental control, and management of comorbidities at each step.<br>Step 2-4: Consider subcutaneous allergen immunotherapy for patients who have allergic asthma. | | | | | |
| | Rescue Medication | • SABA as needed for symptoms – up to 3 treatments at 20-minute intervals initially. Treatment intensity depends on symptom severity.<br>• Consider short course of oral corticosteroids.<br>• Increasing use of SABA or use > 2 days/week for symptom relief (not prevention of EIB) generally indicates inadequate control and the need to step treatment. | | | | | |
| All | Notes | • If an alternative treatment is used and response is inadequate, discontinue it and use the preferred treatment before stepping up.<br>• Theophylline requires serum concentration levels monitoring, zileuton requires liver function monitoring.<br>• LABAs are not indicated for acute symptom relief and should be used in combination with an ICS. | | | | | |

EIB, exercise-induced bronchospasm; ICS, inhaled corticosteroids; LABA, long-acting beta$_2$-agonist; LTRA, leukotriene receptor antagonist

## Panacinar emphysema and Centriacinar emphysema

**There are two types of emphysema that cause clinically significant airflow obstruction:**

| Panacinar emphysema | Centriacinar emphysema |
|---|---|
| • Acini are uniformly involved from level of respiratory bronchiole to terminal blind alveoli. Q<br>• Lesions are more common in lower zone and bases Q<br>• Occurs in association with $\alpha_1$ antitrypsin deficiency Q | • Central or proximal parts of acini formed by respiratory bronchioles are affected whereas distal alveoli are spared Q<br>• Lesions are more severe and common in Upper lobes Q<br>• Occurs predominantly in smokers Q<br>• Is the commonest pattern Q |

## Idiopathic Interstitial Lung Diseases / Idiopathic Interstitial Pneumonias

- Idiopathic Interstitial Pneumonias are *interstitial lung diseases of unknown etiology* that *share similar clinical and radiological features* and are *distinguished primarily by the histopathological pattern on lung biopsy*

| Histologic Name | Clinical Syndrome | Salient Pathological Features |
|---|---|---|
| ***Usual Interstitial Pneumonia (UIP)*** | *Idiopathic pulmonary fibrosis (Cryptogenic fibrosing alveolitis)* | *Temporally and spatially heterogeneous pattern with areas of normal lung, fibroblastic foci, and patchy sub-pleural fibrosis* |
| ***Desquamative Interstitial Pneumonia (DIP)*** | *Desquamative interstitial pneumonia* | *Homogenous intra-alveolar macrophage accumulation. Mild alveolar septal thickening* |
| ***Acute Interstitial Pneumonia (AIP)*** | *Acute interstitial pneumonia (Hamman-Rich syndrome)* | *Homogenous, diffuse lung injury with hyaline membranes, fibroblast proliferation* |
| ***Bronchiolitis Obliterans Organizing pneumonia (BOOP)*** | *Cryptogenic organizing pneumonia, (Idiopathic BOOP)* | *Multifocal organizing pneumonia, with granulation tissue and polyps in alveolar ducts and bronchioles* |
| ***Non-Specific Interstitial Pneumonia (NSIP)*** | *Nonspecific interstitial pneumonia* | *Temporally and spatially homogenous cellular inflammation with mild fibrosis* |
| ***Respiratory Bronchiolitis Associated Lung Disease(RBILD)*** | *Respiratory Bronchiolitis Associated Interstitial Lung Disease* | |

- Detailed Histopathological features are often required to distinguish various forms of Idiopathic Interstitial Pneumonias and hence these have been listed in a tabular form in the following table.

| Pathologic features of Idiopathic Interstitial Pneumonias | | | | | | | |
|---|---|---|---|---|---|---|---|
| ***Feature*** | ***AIP*** | ***BOOP*** | ***DIP*** | ***RBILD*** | ***UIP*** | ***NSIP-Cellular*** | ***NSIP-Fibrosing*** |
| Distribution | *Diffuse* | *Certrilobular* | *Diffuse* | *Mild, focal* | ***Patchy**, Sub-pleural* | *Diffuse* | *Diffuse/panacinar* |
| *Temporal appearance* | *Homogenous* | *Homogenous* | *Homogenous* | *Homogenous* | ***Herterogenous (Variegated)*** | *Homogenous* | *Homogenous* |
| *Septal Inflammation* | Scant | Scant | Scant | None | Scant, patchy | Prominent | Scant. diffuse |
| *Collagen fibrosis* | Absent | Scant | Variable Diffuse | Scant Patchy | ***Characterisitc Patchy*** | Absent | Diffuse |
| *Fibroblast proliferation* | *Diffuse (interstitial)* | *Diffuse (intralumiral)* | *Absent* | *Absent* | ***Fibroblastic Foci prominent*** | *Absent* | ***Fibroblastic Foci Rare*** |
| *Honey-combing* | Absent | Absent | Absent | Absent | Characteristic | Absent | Rare |
| *Alveolar macrophage* | Absent | Absent | Diffuse | Peribonchiolar | Occasional | Occasional | Occasional |
| *Hyaline membranes* | Occasional | Absent | Absent | Absent | Absent | Absent | Absent |

## Asbestos Related Lung Disease

Asbestos Related Lung Disease

| Pulmonary | | Pleural | |
|---|---|---|---|
| Non Malignant | Malignant | Non Malignant | Malignant |
| ***Diffuse Interstitial Fibrosis*** (Asbestosis)<br>*Asbestosis is defined as a diffuse interstial fibrosing disease of lung caused by exposure to asbestos fibres.* | Bronchogenic Carcinoma<br>*All histological subtypes of lung cancer occur with increased frequency but* ***Adenocarcinoma has the highest incidence***[Q] | • ***Pleural plaques***<br>• ***Diffuse Pleural Thickening***<br>• Acute Benign pleural Effusion<br>• Rounded Atelectasis | • ***Mesothelioma***<br>*Both pleural and peritoneal Mesotheliomas develop in persons exposed to Asbestos* |

## Idiopathic Pulmonary Hemosiderosis (IPH)

IPH is a disorder of unknown etiology characterized by recurrent episodes of Diffuse Alveolar Hemorrhage (DAH)

*It has been classically characterized by the triad of iron deficiency anemia, hemoptysis and alveolar infiltrates on chest radiographs.*

Pulmonary Hemosiderosis
(Recurrent episodes of Diffuse Alveolar Hemorrhage)

Characteristic Triad

| *Hemoptysis* | *Iron deficiency Anemia* | *Alveolar infiltrates on chest Radiographs* |
|---|---|---|

## Pulmonary Infiltrates with Eosinophilia (Pulmonary eosiniophilic pneumonia)

### Differential Diagnosis of Pulmonary Infiltrates with Eosinophilia

***Pulmonary infiltrates with eosinophilia:*** (PIE, eosinophilic pneumonias). Constituted by distinct individual syndromes characterized by eosinophilic pulmonary infiltrates and ***peripheral blood eosinophilia.***

**Pulmonary Infiltrates with Eosinophilia (Pulmonary eosiniophilic pneumonia)**

| Etiology Known | Idiopathic |
|---|---|
| *Allergic bronchopulmonary mycoses*<br>*Parastitic infestations*<br>*Drug reactions*<br>*Eosinophilia-myalgia syndrome* | *Loeffler's syndrome*<br>*Acute eosinophilic pneumonia*<br>*Chronic eosinophilic pneumonia*<br>*Allergic granulomatosis of Churg and Strauss*<br>*Hypereosinophilic syndrome* |

## Allergic Bronchopulmonary Aspergillosis

***Allergic bronchopulmonary aspergillosis*** is a pulmonary hypersensitivity disorder caused by allergy to fungal antigens that colonize the tracheobronchial tree. It most commonly occurs in atopic asthmatic individuals in response to antigen of aspergillus species.

| Main diagnostic criteria | Secondary diagnostic criteria |
|---|---|
| 1. *Clinical history of Asthma* $^{Q}$ | 1. *History of brownish plugs in sputum* |
| 2. *Pulmonary infiltrates (transient / fleeting or fixed)* $^{Q}$ | 2. *Indentification / culture of A. fumigatus from sputum* |
| 3. *Peripheral eosinophilia (> 1000 /μL)* $^{Q}$ | 3. *Late skin reactivity to aspergillus antigen – CMDT* |
| 4. *Immediate skin reactivity to Aspergillus antigen (wheal and flare response)* | 4. *Elevated IgE (and IgG) class antibodies specific for A. fumigatus – Harrisons* |
| 5. *Serum precipitins to A. fumigatus* | |
| 6. *Elevated serum IgE levels* $^{Q}$*(>1000ng/ml)* | |
| 7. *Central / proximal bronchiectasis* $^{Q}$ | |

Note

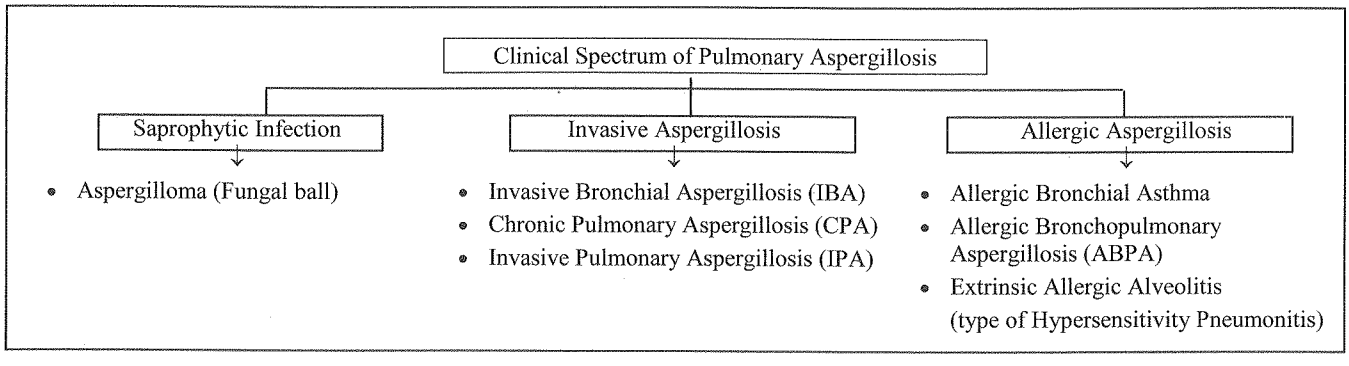
*Elevated IgE (and IgG) class antibodies specific for A. fumigatus has been mentioned as a secondary diagnostic criteria in Harrison's textbook while Fishman's textbook includes this as a main/major diagnostic criteria.*

Criteria for the Diagnosis of ABPA Primary

| Primary |
|---|
| • *Episodic bronchial obstruction (asthma)* |
| • *Peripheral blood eosinophilia (>1000/mm$^3$)* |
| • *Elevated serum IgE concentrations (>1000ng/ml)* |
| • *Immediately type skin reactivity to Aspergillus antigens* |
| • *Precipitating serum antibodies (precipitants) against Aspergillus antigens* |
| • *Elevated serum IgE and/or IgG antibodies specific to A. fumigatus** |
| • *History of pulmonary infiltrates (transient/ fleeting or fixed) on chest radiographs or CT scans* |
| • *Central proximal bronchiectasis on chest CT* |
| **Secondary** |
| • *A. fumigatus in sputum (by repeated culture or microscopic examination)* |
| • *History of expectoration of brown plugs or flecks* |
| • *Arthus reactivity (late skin reactivity) to Aspergillus antigen* |

**Elevated IgE (and IgG) class antibodies specific for A. fumigatus has been mentioned as a secondary diagnostic criteria in Harrison's textbook while Fishman's textbook includes this as a main/major diagnostic criteria.*

**Aspergillus fumigatus is a known cause for bronchopulmonary Aspergillosis**



## Hypersensitivity Reaction to Aspergillus

**Hypersensitivity Reaction to Aspergillus**

*Hypersensitivity Lung diseases that result from exposure to A. Fumigatus allergens include Bronchial Asthma, ABPA and Extrinsic Allergic Alveolitis (Hypersensitivity Pneumonitis)*

| In Atopic Individual | In Non atopic Individuals |
|---|---|
| *Allergic Bronchial Asthma and ABPA* | *Extrinsic Allergic Alveolitis (Hypersensitivity penumonitis)* |
| Allergic Bronchial Asthma and ABPA are seen in atopic individuals and immune response is IgE mediated | Extrinsic Allergic Alveolitis or Hypersensitivity penumonitis is seen in non atopic individuals and immune response is not IgE mediated. Immune response may involve cell mediated (type IV) or immune complex (Type III) reactions. |

## Differentiating features: Bronchial Asthma, ABPA and Extrinsic Allergic Alveolitis

| **Features** | ***Asthma*** | ***ABPA*** | ***Extrinsic allergic alveolitis (Hypersensitive pneumonitis)*** |
|---|---|---|---|
| **Pathology** | *Hypertrophied mucus glands* | *Colonization of airways, viscid mucoid impaction, tissue eosinophilia* | *Lymphocytic infiltration of interstitium, noncaseating granuloma* |
| **Radiological features** | | | |
| **Early** | *Normal, hyperinflation* | *Migratory peripheral infiltrates, atelectasis, bronchiectasis* | *Diffuse alveolar-interstitial infiltrates* |
| **Late** | *Normal, hyperinflation* | *Fibrosis* | *Reticulonodular interstitial opacities* |
| **Skin test reactions to Aspergilus antigens** | | | |
| **Immediate** | *Positive* | *Positive* | *Positive* |
| **Delayed** | *Negative* | *Positive* | *Positive* |
| **Peripheral eosinophilia** | *Negative* | *Positive* | *Negative* |
| **IgG Aspergillus precipitins** | *Positive (upt o 25%)* | *Positive* | *Positive* |
| **Serum IgE levels** | *Normal or mildly elevated* | *Marked deviation* | *Normal* |

## Tropical Pulmonary Eosinophilia

*Tropical Pulmonary Eosinophilia (TPE) is a distinct syndrome that develops in individuals infected with Lymphatic filarial species.*

Clinical symptoms result from allergic and inflammatory reaction elicited by the cleared parasites.

### Features of Tropical Pulmonary eosinophilia (TPE) :

- Male more commonly affected than females (4 : 1)
- History of resistance in filarial endemic region
- ***Paroxysmal cough and wheezing that are usually nocturnal*** $^{Q}$
- Weight loss, low grade fever, adenopathy
- ***Eosinophilia > 3000 eosinophilia / μL*** $^{Q}$
- ***Chest X-Ray : increased bronchovascular markings*** $^{Q}$ *, diffuse miliary lesions* $^{Q}$ , or ***mottled opacities***.
- *Restrictive changes on Pulmonary function test* $^{Q}$
- *Elevated levels of IgE* $^{Q}$ & Antifilarial antibody titers.

***In TPE, Microfilaria are rapidly cleared from the blood stream by the lungs. Thus, microfilariae are sequestrated in the lungs and are not found in the blood.***

## Typical Air Space Pneumonias and Atypical Pneumonias

| AIR Space Penumonia (Typical Pneumonia) | Interstitial Pneumonia (Atypical Pneumonia) |
|---|---|
| Exudate in alveoli i.e. consolidation | No exudate, alveoli are air filled i.e. no consolidation (Infiltrate in interstitium) |
| Infiltrate is primarily of neutrophills (PMN) | Infiltrate is primarily lymphocytic |
| Agents responsible are extracellular | Agents responsible are intracellular |
| Cough is productive of purulent sputum | Cough is dry |
| Chest X-ray shows alveolar pattern | Chest X-ray shows interstitial pattern |
| **Causes of Typical pneumonias**<br>• *Staphylococcal*<br>• *Pneumococcal (Streptococcus Pneumoniae)*<br>• *Kleibsella*<br>• *Pseudomonas*<br>• *Anaerobic Bacteria*<br>• *Other Bacterial* Pneumoniae | **Causes of Atypical pneumonias**<br>• *Mycoplasma pneumonias*<br>• *Viral pneumonias –*<br>*Influenza, RSVAdenovirus, Rhinovirus, Rubeola, Varicilla, Corona*<br>• *Chlamydia pneumonia*<br>• *Coxiella burnetti*<br>• *Pneumocystis carinii*<br>• *Legionella* |

## Typical Bacterial Pneumonias associated with cavitation

*Bacterial Pneumonas associated with cavitation: Review*

- *Staphylococcus*[Q]
- *Kleibsella*[Q]
- *Pseudomonas*[Q]
- *Anaerobic bacteria*

## Characteristic Feature of Stapylococcal Pneumonias

*Bacterial Pneumonas associated with cavitation: Review*

- *Cavitation*[Q] *(single or Multiple thick walled cavities) (may be Bilateral)*
- *Pneumatoceles*[Q] *(Thin walled cystic spaces that may contain air fluid levels)*
- *Pleural Effusion*[Q] */ Empyema*[Q] *with or without bronchopleural fistulas (Pyopneumothorax)*
- *Abscess formation*[Q]

## Classic Histopathology in atypical pneumonia caused by Pneumocystis Pneumonia

### Classic Histopathology in Pneumocystis Pneumonia

**Intra- Alveolar Changes**

Prominent Eosinophilic foamy, vacuolated intraalveolar exudate (HE staining)

- Intra alveolar exudate contains the organisms, which can be identified in various stages of development (trophozoite and cystic stage) by the use of special stains such as
  - Methamine silver / Toluidine stain
  - Wright Giemsa stain
  - Papanicolaou's stain
- Intraalveolar exudate also contains host serum proteins, debris, & surfactant proteins

Alveolar macrophages are present but not prominent in phagocytosis of organism.

- The principle host effector cells against pneumocystis are alveolar macrophages which ingest & kill the organism

**Interstitial Changes**

Mild interstitial Pneumonitis

- Mononuclear interstitial cell infiltrate (mild)
- Damaged type I Pneumocytes
- Hypertrophy /proliferation of type II pneumocytis (Reparative response) *Pneumocystis attaches to, and damages type I pneumocytes. There is associated compensatory hypertrophy of type II pneumocytes.*

Note:
*Most compromised hosts display a mild mononuclear interstitial cell infiltrate however malnourished children display an intense interstitial plasma cell infiltrate which was responsible for the diseases early name of interstitial plasma cell pneumonia'*

## Legionnaire's disease:

- Legionnaires disease presents as an '***atypical pneumonia***'[Q] where a gram stained smear of sputum does not show organisms (Caused by *Legionella).*

| **Legionella** |
|---|
| • ***Legionella*** *is a gram negative [Q], motile [Q], non-encapsulated bacilli [Q], classified under a miscellaneous group* |
| • *Man-to-Man transmission does not occur with Legionella.* [Q] |
| • *No animal reservoirs occur.* [Q] |
| • *Disease is limited to humans.* [Q] |
| *Legionella survive and multiply inside free-living amoeba and protozoa, distributed in natural reservoirs such as stagnant waters [Q], mud and hot spring.* |

- Human infection is typically acquired by *inhalation of aerosols, which form the only source of infection.*[Q]
- Smoking and immunocompromised status are known risk factors.
- The disease occurs with *unusual frequency among patients with hairy cell leukemia* but not among patients with other types of leukemia

| **Common Risk factors for Legionnaires disease** |
|---|
| • *Advancing age* |
| • *Immunocompromised patients:* |
| - *Transplant recipients, HIV, Glucocorticoid recipients* |
| - *Hairy cell leukaemia (monocyte deficiency and dysfunction)* |
| • *Chronic lung disease* |
| • *Smokers* |
| • *Diabetes mellitus (Javetz)* |

- Presents as mild cough slightly productive sputum, sometimes streaked with blood, along with high fever and nonspecific symptoms such as malaise, fatigue, anorexia & headache.

| *Think about the diagnosis as Legionaire's disease whenever the question talks about a pneumonia like picture along with any of the these :* |
|---|
| a. *Occurrence of illness in immunocompromised [Q], smokers [Q] or those with chronic lung disease [Q], or* |
| b. *Occurance of illness in an environment where potable water supply is known to be contaminated with Legionella* |
| c. *Onset of symptoms within 10 days of discharge from a hospital (I.P. 2 to 10 day), or* |
| d. *High fever, [Q] or* |
| e. *Gastrointestinal difficulties like diarrhea, [Q] or* |
| f. *Neurological abnormalities like confusion or altered Sensorium, [Q] or* |
| g. *Numerous neutrophils but no organisms revealed by gram staining of respiratory secretions, or* |
| h. *Hyponatremia [Q] is more common in Legionnaire's, than in any other form of pneumonia, or* |
| i. *Failure to respond to β-lactam drugs [Q] (penicillin or cephalosporins) and aminoglycosids antibiotics.* |

- ***Azithromycin and Respiratory Quinolones are the drugs of choice for Legionnaire's disease***

Drugs of choice for Legionnaire's Disease

| **Newer Macrolides** | **Respiratory Quinolones** |
|---|---|
| • *Azithromycin* | • *Levofloxacin* |
| | • *Moxifloxacin* |
| | • *Gatifloxacin* |
| | • *Gemifloxacin etc.* |

# Tuberculosis: Congenital Tuberculosis and Primary Tuberculosis

## Congenital Tuberculosis

- *True congenital Tuberculosis is defined as tuberculosis occurring in infants as a result of infection with M. Tuberculosis during intrauterine life.*
- Three modes of fetal infection have been proposed
  a. Transplacental (Hematogenous infection via the umbilical vein)
  b. Fetal aspiration of infected amniotic fluid
  c. Fetal ingestion of infected amniotic fluid

**Congenital Tuberculosis**

| Congenital Tuberculosis caused by ***Transplacental spread*** (Hematogenous) | Congenital Tuberculosis caused by ***aspiration of infected amniotic fluid*** | Congenital Tuberculosis caused by ***ingestion of infected amniotic fluid*** |
|---|---|---|
| Most common Primary site of infection is Liver (Hematogenous infection leads to miliary disease) | Most common Primary site of infection is Lungs | Most common Primary site of infection is Gastrointestinal Tract |
| Since Lungs are eventually involved in most cases of congenital tuberculosis where Liver is the primary site of infection, Lungs are the most commonly involved sites in Congenital Tuberculosis | | |

- When infection enters the fetus through the umbilical veins, the primary tubercular lesions (primary complex) develop in the liver. *(Lesions may also develop in the lungs suggesting further passage of bacilli through the ductus venosus)*

> ***'The only lesion in the neonate that is unquestionably associated with congenital infection is a primary complex in the liver; all others may be acquired congenitally or postnatally***

- When infection enters the fetus through the aspiration / inhalation of infected amniotic fluid the primary lesions (primary complex) develops in the lungs.

  *Tuberculous involvement of Lungs without associated hepatic lesions indicates aspiration of infected ammotic fluid on inhalation of tubercle bacilli.*

> ***Lungs are the most common organs involved in congenital tuberculosis being involved almost all cases***

- *Congenital Tuberculosis is charachterized by a nonimmune, non-reactive response with abundant caseation and an unsually large number of bacilli. There may be multiple foci of infection within the primary site and the distribution is usually miliary.*

**Diagnostic Criteria for Congenital Tuberculosis**

| Beitzke' Criteria (1935) | Revised Criteria by Cantwell (1994) |
|---|---|
| i. Bacteriological Proof of Tuberculosis<br>***ii. Primary complex in Liver***<br>iii. If primary complex is lacking in Liver then tuberculosis can be considered congenital only if:<br>a. Tuberculous lesions present in fetus or newborn are only few days old<br>b. Or in an older infant extrauterine infection can be excluded with certainity | i. Lesion in first week of life<br>***ii. A primary hepatic complex or caseating hepatic granuloma***<br>iii. Tuberculous infection of placenta or maternal genital tract<br>iv. Exclusion of possibility of postratal transmission by a thorough investigation of contacts including the infant's hospital attendants or birth attendants |

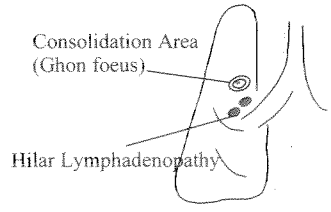
## Primary tuberculosis:

- *It is the first infection with tubercle bacilli in individuals who have not been previously exposed to the organisms*
- *Seen in children* Q
- Primary complex is characteristic

**Primary (Ghon) complex**
- Unilateral enlarged hilar lymph nodes Q
- Ghon focus Q: Epitheloid-cell granulomatous inflammation (consolidation) at site of parenchymal infection. Usually small and subpleural most commonly located under pleura in lower part of upper lobe

- Usually a symptomatic Q or manifested by a mild flu like illness at time of tuberculin conversion
- Lesion heal by fibrosis Q and may calcify Q
- Radiological evidence of healed primary infection may or may not be present Q

**Effects of primary tuberculosis**
- Tuberculin positivity Q
- Partial immunity to tuberculosis Q: individual requires a higher dose to be reinfected by tubercle bacilli
- Presence of dormant tubercle bacilli




**Tuberculous Primary Infection**
↓
Primary complex
**Consolidation**
(*Ghon focus*: Unilateral solitary *area of tuberculous consolidation* under the pleura in the lower part of upper lobe)
**Hilar Lymphadenopathy**
↓
Healing
Heals by ***fibrosis*** or calcification

## Montoux test

Montoux test is carried out by injecting one tuberculin unit (1TU) of PPD in 0.1 ml on the flexor surface of forearm (PPD RT 23 with Tween 80)

↓
**Test is read after 72 hours** Q *(not 48 hours)*
↓
Look for Erythema and Induration Q

| < 6 mm | 6 – 9 mm | > 10 mm |
|---|---|---|
| *Negative* Q | ***Doubtful*** Q | *Positive* Q |

- ***A positive test indicates that patient is infected with M. tuberculosis. It does not however prove that the person is 'suffering' from the disease*** – *Park*
- ***Studies indicate that 92% of new cases occur in persons who already are tuberculin reactors***.– *Park*
- ***6-9 mm induration does not indicate high chances of developing tuberculosis.*** Infact patients with 25 mm induration have more chances of developing tuberculosis than those with 6-9 mm induration - *Park*

**Causes of False Negative Tuberculin Tests (Anergy)**

False negative tuberculin tests (Anergy) may occur in situations such as :
- *Miliary tuberculosis* Q
- Convalescence from some viral infections like *Measles* Q
- Lymphoreticular malignancy
- *Sarcoidosis* Q
- *Severe malnutrition* Q
- *Immunosuppressive therapy* Q
- *Defective cell mediated immunity* Q

## Sources of Bleeding in Hemoptysis

**Sources of Bleeding in Hemoptysis**

| *Bronchial Arteries* | *Pulmonary Arteries* |
|---|---|
| *Most common source of Bleeding in Hemoptysis (>90% cases)* | *Uncommon source of Bleeding in Hemoptysis (<10% cases)* |

*A pulmonary arterial source should be considered in addition to the more common systemic source (bronchial artery) in the setting of destructive lung lesion such as cavitatory tuberculosis. However the vascular structure that should be evaluated first is the bronchial artery.*

**Remember: Ramussen Aneurysm**

- Ramussen aneurysm is a rare cause of bleeding in cavitatory tuberculosis and results from erosion of tuberculous cavity into a pulmonary artery branch.
- *The most common source of bleeding in Remussen aneurysm is the pulmonary artery*[Q].

## Facts to Remember about Hemoptysis

| | |
|---|---|
| *The most common cause of Hemoptysis* | *Bronchitis and Bronchogenic CA*[Q]<br>*(Bronchitis > Bronchogenic CA)*[Q] |
| *The most common causes of Hemoptysis in India* | *Tuberculosis*[Q] |
| *The most common cause of Massive Haemoptysis* | *Bronchectasis (World wide)*[Q]<br>*Tuberculosis(India)*[Q] |

## Sarcoidosis

- Sarcoidosis is a chronic multisystem disorder of unknown cause characterized by accumulation of T lymphocytes and mononuclear phagocytes in various tissues of body
- The inflammatory process in sarcoidosis is characterized by formation of sarcoid granulomas in various organs.
- Giant Cells within granulomas can be of '*Langerhan's or Foreign body variety*' and often contain inclusions bodies

Inclusions seen in giant cells in sarcoidosis. (Remember as **SAR**coidosis)
- ***S**chaumann bodies*[Q]
- ***A**steroid bodies*[Q]
- ***R**esidual bodies*[Q]

- Non-caseating **SAR**coid granulomas can affect several organ or organ systems

Non caseating **SAR**coid granulomas in affected organs

| **Lung (90%)** | **Lymph nodes (75-90%)** | **Skin** | **Others** |
|---|---|---|---|
| • ***Interstitial lung disease***[Q] Fibrosis of lung parenchyma<br>• Pleura is involved in 1-5% of cases u/e ***pleural effusion***[Q]<br>• *Cavitation* ***is rare***[Q] | • B/L hilar lymphadenopathy is the hallmark of sarcoidosis<br>• Parotid enlargement B/e involvement is the vuli | • ***Erythema nodosum***[Q]<br>• ***Lupus perenium***[Q] (purple blue shiny swollen lesions on nose, cheeks, lips, ears). | *Eye* Uveitis<br>*Kidney (rare)* Renal hypercalcemia with or without hypercalcuria<br>*Skeletal* Arthritis<br>*Nervous system* Peripheral neuropathy.<br>*Heart* Cor pulmonle |

- ***Bilateral hilar lymphadenopathy is the hallmark of disease***

| **The three classic x-ray pattern of pulmonary sarcoidosis are** | |
|---|---|
| • *Type I* | : *B/L hilar lymphadenopathy with no parenchymal changes* |
| • *Type II* | : *B/L hilar lymphadenopathy with diffuse parenchymal changes* |
| • *Type III* | : *Diffuse parenchymal change with no hilar lymphadenopathy.* |

- *Sarcoidosis has a variable course. Disease clears spontaneously in 50% of patients – Harrisons 16th/2023*
- *Tuberculin test may be negative due to the presence of skin anergy – Harrisons 16th/2023*

**Diagnostic tests for sarcoidosis have often been asked**

| *Ancillary* | *Confirmatory* |
|---|---|
| • Blood: ***ACE***$^{Q}$<br>• ***X ray chest***$^{Q}$<br>• ***Skin test for anergy***$^{Q}$<br>• ***Gallium 67 etc.***$^{Q}$ | • Biopsy |

| | |
|---|---|
| ***X-Ray chest***: | • Bilateral hilar lymphadenopathy is the hallmark of disease<br>• Parenchymal involvement may or may not be present ***(clear lung fields)***$^{Q}$<br>• ***Egg shell calcification of hilar nodes may be seen***$^{Q}$ |
| ***Kveim siltzbach test***$^{Q}$***:***<br>***Skin test***$^{Q}$***:*** | • Intradermal injection of a heat treated suspension of a sarcoidosis spleen extract. |
| ***Angiotensin converting enzyme (ACE) in blood***$^{Q}$***:*** | • ACE is elevated in 2/3 of patients with sarcoidosis $^{Q}$ (60%) $^{Q}$<br>• ACE levels indicate activity of disease$^{Q}$<br>• ACE levels provide an important method of monitoring the course of disease.$^{Q}$<br>*(The cells in granuloma release angiotensin converting enzyme into the serum)* |
| ***Gallium 67 scan***: | • Gallium 67 lung scan is usually abnormal showing a pattern of diffuse uptake |
| ***Bronchoalveolar lavage*** | • Lavage fluid is characterized by<br>*-increase in Lymphocytes*$^{Q}$<br>*-high CD4 / CD8 cell ratio*$^{Q}$ |
| ***Biopsy***: | • Biopsy is mandatory to make a definitive diagnosis of sarcoidosis<br>• Characteristic finding is a typical non casseating granuloma$^{Q}$ |
| ***Lung function*** | • Typical for interstitial lung disease. |

# Acute/Adult Respiratory Distress syndrome (ARDS)

## Synonyms used for Acute/Adult Respiratory Distress syndrome.

**Synonym: for ARDS** *(Taken from 'Pathology of Lung')*

- *Shock lung*
- *Blast lung*
- *Traumatic wet lung*
- *Congestive Atelectasis*
- *DoNang Lung*
- *Noncardiogenic Pulmonary Edema*
- *Diffuse Alveolar Damage*

## Clinical disorders associated with lung injury/ ARDS

| Direct lung injury | Indirect lung injury |
|---|---|
| • Pneumonia<br>• Aspiration of gastric contents<br>• Pulmonary contusion<br>• Near drowning<br>• Toxic inhalation injury | • Sepsis<br>• Severe trauma: - Multiple bone fractures<br>- Head trauma<br>- Flail chest<br>• Burns<br>• Multiple transfusions<br>• Drug overdose: eg Narcotic overdose<br>• Pancreatitis<br>• Post-cardiopulmonary bypass |

| Miscellaneous causes for ARDS |
|---|
| • *Renal failure*<br>• *Liver failure*<br>• *Disseminated intravascular coagulation*<br>• *Ecclampsia*<br>• *Amniotic fluid emboli / Air emboli*<br>• *Hanging*<br>• *High altitude* |

## Pathophysiology features and diagnostic criteria for ARDS

**ARDS is an acute form of lung injury characterized by:**

- Increased permeability of alveolar capillary membrane.
- ***Diffuse alveolar damage.***
- Accumulation of proteinaceous pulmonary edema (non cardiogenic pulmonary edema $^{Q}$)

**Diffuse alveolar damage (ARDS)**
Alveolar closure and collapse
(Exaggerated by reduction in surfactant due to *injury to type II pneumocytes*)
↓
***Reduced compliance*** of Lung as a whole $^{Q}$
(*Stiff lung*)
↓
***Diminished tidal volume*** $^{Q}$
Worsened gas exchange
*(Pulmonary edema + Hyaline membrane (fibrin + coagulated cell debris)*
***Hypoxemia*** $^{Q}$
↓
Increased Respiratory frequency
↓
$CO_2$ washout and ***Hypocapnia***

## Features of ARDS

| Clinical /Physiological |
|---|
| • Clinical history of insult known to cause ARDS<br>• Clinical exclusion of chronic lung disease and Left ventricular failure<br>• ***Diffuse alveolar damage.***<br>• *Reduced surfactant (Injury to type II pneumocytes)*<br>• Increased permeability of alveolar capillary membrane.<br>• Accumulation of *proteinaceous pulmonary edema* (non cardiogenic pulmonary edema Q)<br>• Pulmonary edema + ***Hyaline membrane*** (fibrin + coagulated cell debris)<br>• ***Reduced compliance*** (*stiff lung*)<br>• ***Diminished tidal volume*** Q<br>• ***Hypoxemia*** Q (Worsened gas exchange d/t ***pulmonary shunting***)<br>• ***Hypocapnia*** Q ($CO_2$ washout) |

| Diagnostic Criteria (ARDS) | |
|---|---|
| $PaO_2/FiO_2$ | *≤200 mm Hg* |
| Onset | *Acute* |
| Chest Radiograph | *Bilateral Alveolar or Interstitial infiltrates* |
| Absence of Left Atrial Hypertension | • *PCWP≤18 mmHg*<br>• *No clinical evidence of increased left atrial pressure* |

### Differentiating Features between Acute Lung Injury (ALI) and ARDS

*Acute Lung Injury (ALI) is a less severe disorder than ARDS but has the potential to evolve into ARDS. ALI can be differentiated from ARDS by the arterial $PO_2/FiO_2$ (Inspiratory $O_2$ fraction) ratio.*

| Diagnostic Criteria | ALI | ARDS |
|---|---|---|
| $PaO_2/FiO_2$ | *≤300 mm Hg* | *≤200 mm Hg* |
| Onset | *Acute* | *Acute* |
| Chest Radiograph | *Bilateral Alveolar or Interstitial infiltrates* | *Bilateral Alveolar or Interstitial infiltrates* |
| Absence of Left Atrial Hypertension | • *PCWP≤18 mmHg*<br>• *No Clinical evidence of increased left atrial pressure* | • *PCWP≤18 mmHg*<br>• *No clinical evidence of increased left atrial pressure* |

## Pulmonary Thromboembolism

***Sudden onset of dyspnea and chest pain following surgery or immobilization, strongly suggests a diagnosis of pulmonary thromboembolism.***

### Classic Presentation of Pulmonary Thromboembolism

- *The most frequent symptom of PE is dyspnea* Q
- *The most frequent sign of PE is tachypnea* Q
- *Symptoms based on Size of Embolus*

| Symptoms suggesting massive PE | Symptoms suggesting small emboli located distally |
|---|---|
| *Dyspnea* | *Pleuritic pain* |
| *Syncope* | *Cough* |
| *Hypotension* | *Haemoptysis* |
| *Cyanosis* | |

## Classic Abnormalities on ECG in pulmonary Embolism

- *Sinus Tachycardia (Commonest : OHCM)*
- *Right ventricular strain pattern (T wave inversion in leads V1 to V4 perhaps most frequent - Harrison)*
- *$S_I Q_{III} T_{III}$ Pattern : (Classic pattern but rare (OHCM))*

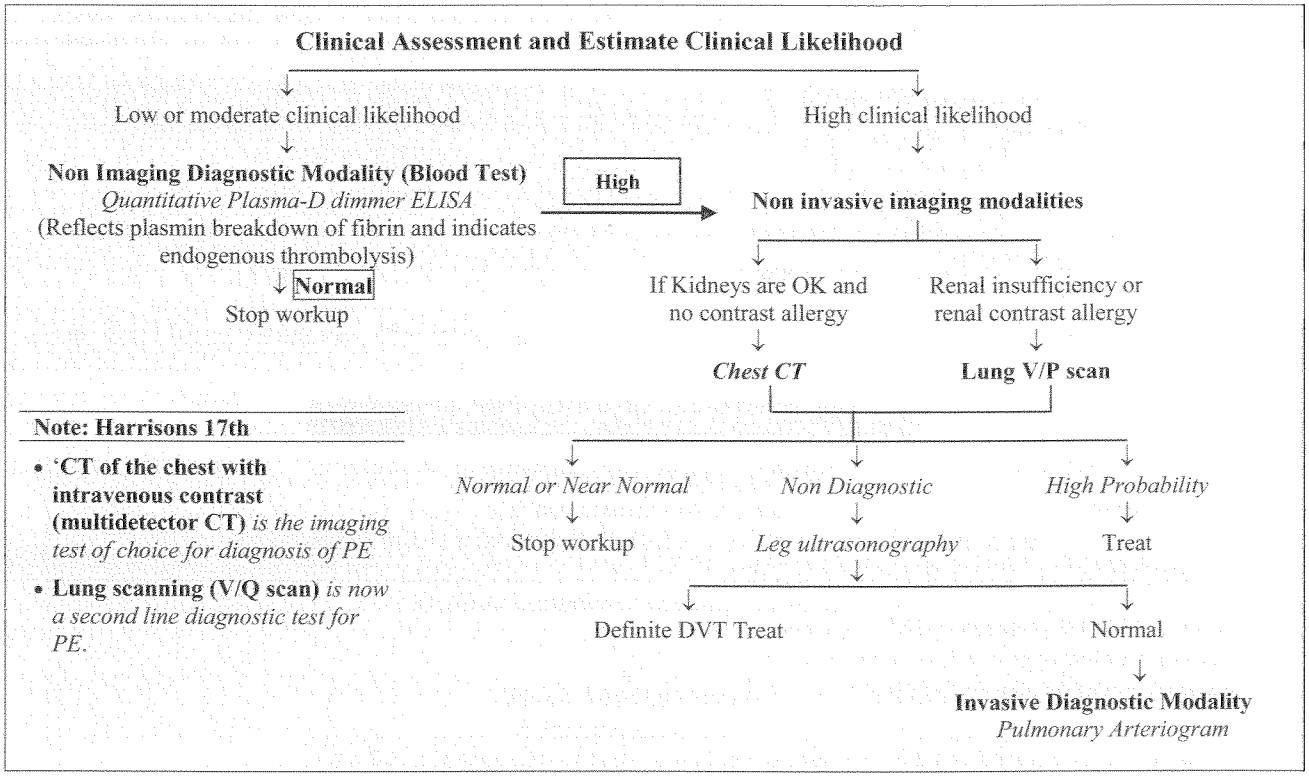
  - Deeps S waves in lead I
  - Q wave
  - Inverted T wave in lead III

- *New onset Atrial Fibrillation / Atrial Flutter.*
- *Right Axis Deviation / RBBB.*

## Diagnostic Strategy in cases of suspected Pulmonary Thromboembolism

| Most definitive / specific test for PE [Q] | Best initial imaging test for diagnosis of PE [Q] |
|---|---|
| *Pulmonary angiography* [Q] | *CT scan with intravenous contrast* [Q] *(Preferred choice, against a lung V-Q scan)* |

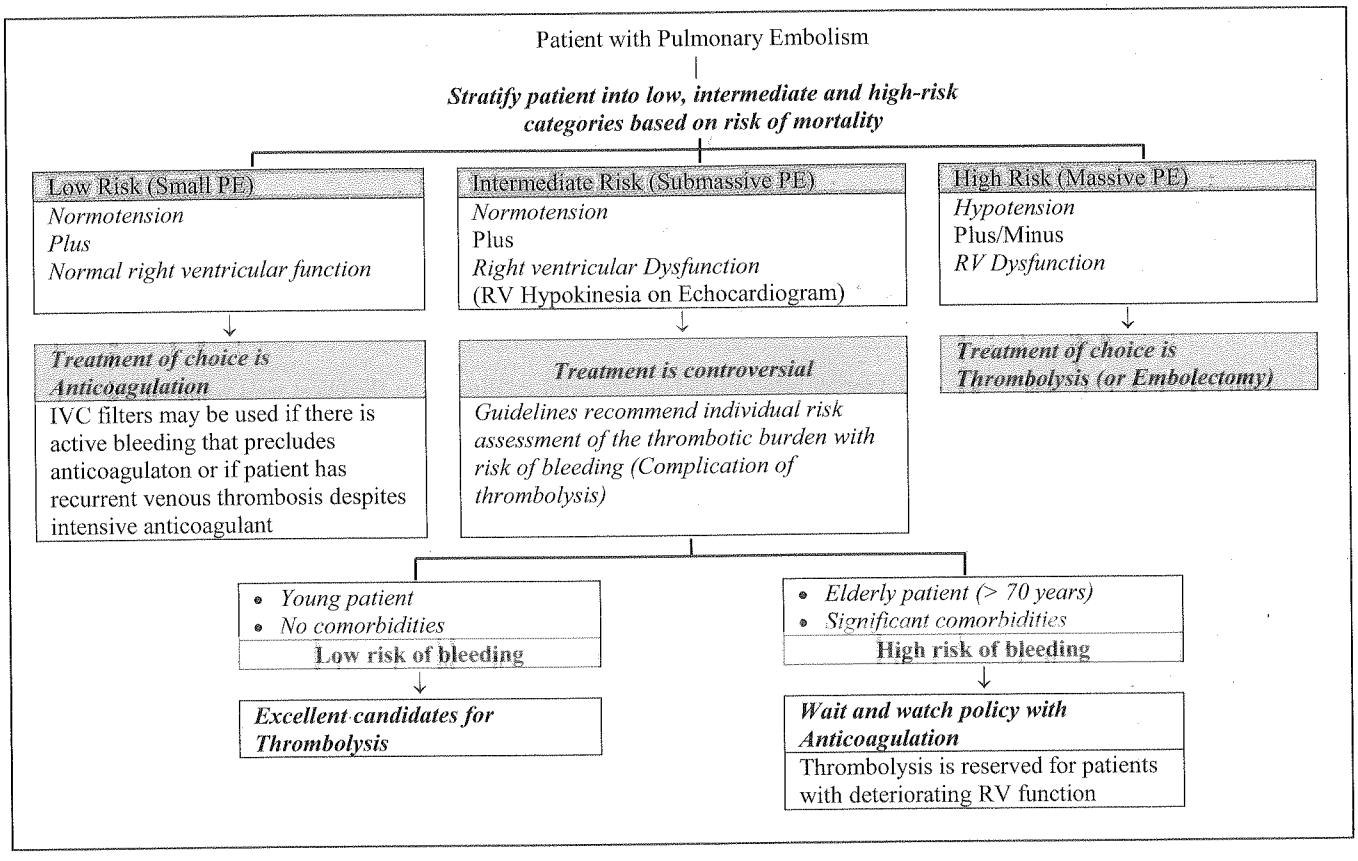
**Clinical Assessment and Estimate Clinical Likelihood of Pulmonary Embolism**




**Note: Harrisons 17th**

- **'CT of the chest with intravenous contrast (multidetector CT)** *is the imaging test of choice for diagnosis of PE*
- **Lung scanning (V/Q scan)** *is now a second line diagnostic test for PE.*

## Treatment of Patients with Pulmonary Embolism based on Risk Stratification




## Pulmonary Hypertension / Idiopathic Pulmonary Arterial Hypertension

**Features of Primary Pulmonary Hypertension / Idiopathic Pulmonary Arterial Hypertension**

- *Most common in Young women* who are 20-40 years of Age (Robbin's 7th/745) (strong female predominance)
- *Most common symptom is exertional dyspnea (predominant symptom is dysnea)*
- Pulmonary Function tests
  - *Are usually normal with the exception of DLCO which is characteristically reduced.*
  - *Non obstructive PFT (FEV1/FVC>0.7 or 70%)*
  - *Non restrictive PFT (FVC > 80%)*
  - *DLCO2 is reduced (↓DLCO)*

(Note: Mild restrictive effects can be seen in upto 20% of patients with advanced IPAH)

**X Ray chest**

- *X Ray chest shows clear lung fileds in PPH/IPAH*
- *X Ray chest usually shows enlargement of pulmonary arteries*

**Exercise tolerance**

- *Exercise tolerance is markedly reduced*

(The exercise capacity of these patients appears to be limited by a low cardiac output because of a decrease in the functional pulmonary vascular bed)

## Cor-Pulmonale

*The most common cause of chronic cor pulmonale is chronic obstructive pulmonary disease - Rubin's pathology*

Cor Pulmonale

| Acute Cor Pulmonale | Chronic Cor Pulmonale |
|---|---|
| *The most common cause is a sudden, massive, pulmonary embolus* | *The most common cause is COPD* |

## Bronchial Breath Sounds

The bronchial breath sound originates in the larger airways and are transmitted directly to the chest wall without passing through the alveoli. The sound passing through the lung tissue is not modified and auscultated like bronchial sounds from the chest walls. This sound resembles the sound obtained by listening over the trachea (directly placing a stethoscope on the trachea).

*The characteristics of these sounds are:*

1. Duration of expiration is equal to or longer than that of inspiration.
2. Intensity of expiration is more than that of inspiration.
3. There is a definite gap between inspiration and expiration.
4. Sounds are harsh or aspirate in nature.
5. They are high-pitched with frequencies above 600Hz.

## Types of Bronchial Breath Sounds

Bronchial breath sounds are of three types: tubular, cavernous, and amphoric.

Bronchial Breath Sounds

| Tubular Bronchial Breath sound | Caveronous Bonchial Breath sound | Amphoric Bronchial Breath sound |
|---|---|---|
| The tubular bronchial breath sound is a high pitched sound resulting from the passage of vibrations produced in the small bronchi directly to the chest wall through a solid lung tissue. This is seen when the lung parenchyma becomes a solid mass, as in consolidation. | The cavernous bronchial breath sounds is a low pitched bronchial breath sound heard over a cavity, which is situated superficially and communicated to a patent bronchus. The size of the cavity should be more than 2 cm in diameter to produce a cavernous breath sound. | The amphoric bronchial breath sounds is a high pitched bronchial sound that resembles the sound produced by blowing air into a wide-mouthed bottle. This is heard over a very large cavity communicating pneumothorax. It is also seen in large pulmonary cysts having communication with a patent bronchus. |

## Clinical Distinguishing Features on Clinical Examination

| | Tracheal deviation (Mediastinal shift) | Chest expansion | Percussion note ↓ Duller ↑ Hyper-resonant | Breath sounds ↑ Louder ↓ Softer | Added sounds | Vocal resonance |
|---|---|---|---|---|---|---|
| **Consolidation** | No | Normal, or↓ | Normal, or↓ | ↑ (Bronchial) | Coarse crackles +/- rub | ↑ Whispering Pectoriloquy |
| **Lobar collapse** | Yes (Towards collapse) | ↓ | ↓ | ↓ | No | ↓ |
| **Pleural effusion** | No | ↓ | ↓ (Stony dull) | ↓ | Occasional rub | ↓ |
| **Pneumothorax** | Yes (Specially with tension) | Normal or↓ | ↑ | ↓ | Occasional click | ↓ |

# Pleural Effusion

## Differential Diagnosis of Pleural Effusion based on predominant side of involvement

| Predominant left sided pleural effusion | Predominant right sided pleural effusion |
|---|---|
| • *Acute pancreatitis* | • *Amoebic liver abscess* |
| • *Oesophageal rupture* | • *Cirhosis of liver* |
| • *Dressler's syndrome (postmyocardial infarction syndrome)* | • *Congestive cardiac failure* |
| | • *Meig's syndrome (fibroma of ovary with ascites ad pleural effusion)* |

## Differential Diagnosis of Pleural Effusion based on pleual fluid biochemical findings

### Pleural Fluid with decreased glucose

**Conditions associated with Decreased Glucose (<60mg/dl) in pleural fluid**

- ***Malignant Effusion***$^{Q}$ *(Also mentioned in Harrisons)*
- ***Rheumatoid Effusion***$^{Q}$ *(Also mentioned in Harrisons)*
- ***Parapneumonic Effusion***$^{Q}$ *(Bacterial Infections as mentioned in Harrisons)*
- *Tuberculous Effusion*$^{Q}$ *(Also mentioned in CMDT)*
- *Hemothorax*
- *Paragonimiasis*
- *Churg-Strauss Syndrome*

| Pleural effusion with low glucose (< 60 mg/dl) |
|---|
| 1. Malignancy |
| 2. Bacterial infections |
| 3. Rheumatoid pleuritis |

### Pleural Fluid with High Amylase

**High amylase level in pleural fluid suggests**

- *Esophageal rupture*$^{Q}$
- *Pancreatic pleural effusion*$^{Q}$ *(Pancreatitis/Pancreaticpseudo cyst)*
- *Malignancy*$^{Q}$ (Adenocarcinoma of lung/pancreas)

### Pleural Fluid with Cholesterol Crystals

**Pleural effusion with cholesterol crystals**

- *Hypothyroidism (myxoedema)*
- *T.B.*
- *Rheumatoid arthritis*

## Characteristics of Tuberculous effusion

**Characteristics of Tuberculous effusion**

- *Exudative*
- *Proteins increased (Pleural fluid protein / Serum protein > 0.5)*
- *Pleural fluid LDH increased (P. Fluid LDH/ Serum LDH > 0.6*
- *Haemorrhagic*
- *Glucose: equal to serum levels; occasionally < 60 mg/dl*
- *WBC count increased: predominantly small lymphocytes*
- *High levels of TB markers in pleural fluid*
  - *Adenosine deaminase > 45 IU/L*
  - *Interferon V > 140 pg/ml*
  - *Positive PCR for tubercular DNA*

# Pneumothorax

## Primary Spontaneous Pneumothorax (Primary pneumothorax)

- ***Primary spontaneous penumothorax occurs in persons with no clinical evidence of lung disease and often without an obvious precipitating event***
- Most of these patients have occult lung disease (sub clinical lung disease) in the form of subpleural apical blebs (recognized on CT scan)
- *Characteristic risk factors include a positive family history and history of smoking (occurs almost exclusively in smokers according to Harrisons)*
- *Characteristically affects tall, thin boys and men between the age of 10 and 30 years*
- *Left-sided pneumothorax is associated with right axis deviation.*

| **Primary Spontancous pneumothorax** |
|---|
| • *No clinical evidence of pre existing lung disease*[Q] |
| • *Rupture of apical subpleural blebs*[Q] |
| • *Positive family history*[Q] |
| • *History of smoking*[Q] |
| • *Tall and thin individual* [Q] |
| • *Young adults (10 to 30 years of age)* [Q] |
| • *Male gender*[Q] |

## Iatrogenic Pneumothorax

### Common Causes of Iatrogenic Pneumothorax

| Common causes of Iatrogenic Pneumothorax (Decreasing order of frequency) |
|---|
| • *Transthoracic Needle Lung Biopsy* |
| • ***Subclavian vein cannulation*** |
| • *Thoracocentesis* |
| • *Pleural Biopsy* |
| • *Positive Pressure ventilation* |

### Presentation of Iatrogenic Pneumothorax

Iatrogenic Pneumothorax

| History |
|---|
| • History of Procedure known to cause iatrogenic pneumothorax (subclavian vein cannulation) |
| • Sudden onset Breathlessness |
| • Chest discomfort / chest pain |

| Examination |
|---|
| Inspection/ palpatum |
| • Reduced movements over affected side |
| • Mediastinal shift to opposite side |
| • Decreased vocal fremitus |
| Percussion |
| Hyper-resonant |
| Auscultation |
| Diminished or absent breath sound |

# Sleep Apnea

## Sleep Apnea

- Sleep Apnea is defined as an intermittent cessation of airflow at the nose and mouth during sleep
- ***By definition/convention breath cessation for at least 10 seconds is termed Apnea***

> *By convention sleep apnea is defined by breath cessation for at least 10 seconds. Most patients with sleep apneas have cessation for 20-30 seconds. The duration of breath cessation may be as long as 2-3 minutes.*

- Sleep apneas can be central or obstructive

| Central sleep Apnea | Obstructive sleep Apnea |
|---|---|
| Sleep apnea occurs due to transient cessation of neural drive to all respiratory muscles | Sleep Apnea occurs due to transient occlusion of the orapharyngeal airway despite continued respiratory drive |

# Primary pulmonary hypoventilation

**Characterized by:**

*Impaired chemoreception resulting in decreased ventilatory drive.*

Chronic hypercapnia and hypoxemia in the absence of identifiable neuromuscular disease or mechanical ventilatory impairment.

**Presentation :**

Occurs in all age groups but majority of cases have been reported in males aged 20-50 years.

Early: lethargy, fagtigue, daytime somnolence, disturbed sleep and morning headache.

Late: Cyanosis polycythemia, pulmonary hypertension, congestive heart failure.

Note : Dyspnea is uncommon despite severe arterial blood gas derangements because of impaired chemotherapy.

**Diagnosis :**

The key diagnostic feature is respiratory acidosis in the absence of respiratory muscle weaknesses or impaired ventilatory mechanics.

## Bronchogenic Carcinoma: Lung Cancer

| Histological type | Frequency (Worldwide) | |
|---|---|---|
| *Adenocarcinoma* | *32%* | • ***Most common Bronchogenic Carcinoma in India is squamous cell carcinoma*** |
| *Squamous cell ca* | *29%* | • ***Most common Bronchogenic Carcinoma worldwide is Adenocarcinoma*** |
| *Small cell carcinoma* | *18%* | |
| *Large cell carcinoma* | *9%* | |
| *Carcinoid* | *1%* | |

### Facts to remember about Bronchogenic Carcinoma

- *Most frequent histological type* : *Adenocarcinoma*
- *Most frequent histological type in India* : *Squamous cell carcinoma*
- *Most common histological variety in life time non-smokers* : *Adenocarcinoma*
- *Most common histological variety in young patients.* : *Adenocarcinoma*
- *Most common histological variety in females* : *Adenocarcinoma*
- *Most common site for metastasis from Ca lung* : *Liver (page 521 H)*
- *Most common endocrine organ to be involved by metastasis from Ca lung* : *Adrenals.*
- *Ca lung which metastizes to opposite lung* : *Adenocarcinoma.*
- *Commonest tumor to metastise to heart* : *Ca lung (Bronchogenic Ca)*
- *Histological varieties that cavitate* : *Squamous cell and large cell.*
- *Histological varieties that are central in distribution* : *Squamous cell and small cell.*
- *Histological varieties that are peripheral in distribution* : *Adenocarcinoma.*
- *Pancoast tumor is histologically* : *Squamous cell.*
- *Most common variety associated with paraneoplatic syndrome* : *Small cell variety.*
- *Most common variety associated with hypokalemia* : *Small cell (presumably d/t ACTH)*
- *Most common variety associated with hypercalcemia* : *Squamous cell (presumably d/t PTH)*
- *Histological variety most responsive to chemotherapy* : *Small cell*
- *Histological variety response to Radiotherapy* : *Small cell*
- *Histological variety associated with best prognosis* : *Squamous cell*

## Small cell carcinoma vs Non-small cell carcinoma

| Property | **Small cell carcinoma**<br>• *Oat cell Carcinoma* | **Non small cell Carcinoma**<br>• *Squamous cell carcinoma*<br>• *Adenocarcinoma*<br>• *Large cell carcinoma*<br>• *Bronchoalveolar carcinoma* |
|---|---|---|
| Location | • ***Central location*** | • *Peripheral location* |
| | **Central location**[Q]<br>• *Squammous cell*[Q]<br>• *Small cell*[Q] | **Peripheral location**[Q]<br>• *Adenocarcinoma*[Q]<br>• *Large cell variant*[Q] |
| Cavitation | • ***Rare*** | • *Common in Squammous Cell*<br>• *Also seen in Large Cell* |
| | **Cavitatory variant**<br>• *Squamous cell (most common)*<br>• *Large cell* | **Non cavitatory variants**<br>• *Small cell*<br>• *Adeno carcinoma* |
| Metastasis | • ***Highly metastatic lesion*** with widespread metastasis at time of diagnosis<br>• Common site of metastasis include brain, bone, Liver and adrenals | Less metastatic than small cell carcinomas |
| Paraneoplastic syndrome | • *ACTH*<br>• *ADP (Vasopressin)*<br>• *Calcitonin*<br>• *ANF*<br>• *Gastrin Releasing peptide* | • ***PTH*** |
| Response to chemotherapy | ***Superior Response***<br>***Overall regression rate is 90%***<br>Rate of complete regression is 30% | Inferior Response<br>*Objective shrinkage in 30-50%*<br>Complete response : uncommon |
| Response to Radiotherapy | ***Superior Response***<br>*Objective Shrinkage in 80-90%*<br>*Complete response: Often* | Inferior Response<br>*Objective shrinkage in 30-50%*<br>*Complete response: Uncommon* |
| Primary management | *Managed primarily with Chemotherapy with or without Radiotherapy* | *Management primarily with Surgery or Radiotherapy (localized lesions)* |
| | • *Small cell lung carcinomas behave as systemic disease.*<br>• Most small cell carcinomas have already spread at the time of presentation beyond the bounds of surgery and they are *managed primarily by chemotherapy with or without radiotherapy*<br>***Small cell carcinomas are highly chemosensitive with an overall 90% regression rate with chemotherapy.*** | *For non small cell carcinomas the primary modality depends on the extent of disease*<br>• **Localized diseases: (Stage I & II)**<br>Primary modality of treatment is surgery **pulmonary resection.**<br>• **Advanced disease:**<br>**Radiotherapy with curative intent** is advocated<br>(± chemotherapy)<br>• **Metastatic disease (Stage IV)**<br>symptomatic/supportive |

**Cavitation is a feature of squammous cell and large cell variants and not of oat cell/small cell variant**

*'In contrast to squammous cell carcinoma in which central cavitation is noted in 10-20% of cases, small cell cancer rarely cavitates' - Clinical Hematology & Oncology (2003)/945*

**Adenocarcinomas present as peripheral masses and not as central masses**

*'Squammous and small cell cancers usually present as central masses while adenocarcinoma and large cell cancers tend to present as peripheral nodule and masses' – Harrison*

## Presenting Symptoms of Bronchogenic Carcinoma

*The most common presenting symptom of lung cancer is cough – Robbins*

| Common presenting symptoms of lung cancer (Robbins) | Common presenting symptoms of lung cancer (*General Thoracic Surgery*) In decreasing order of frequency. |
|---|---|
| ***Cough (75%-Commonest)*** | ***Cough (commonest)*** |
| Weight loss (40%) | Hemoptysis |
| Chest pain (40%) | Chest pain |
| Dyspnea (20%) | Dyspnea |
| | Wheezing or strider |
| | Hoarseness |
| | Pleural effusion |
| | Superior vena caval syndrome |
| | Pancoast tumour |
| | Dysphagia |
| | Phrenic palsy |

## Superior vena caval syndrome (SVC syndrome)

- SVC syndrome results from an impedance in outflow from superior vena cava due to external compression
- *The most common cause of SVC syndrome is external compression by a malignant tumour*[Q]
- *The most common malignant tumor causing SVC syndrome is bronchogenic carcinoma*[Q]
- *The most common histological type of bronchogenic carcinoma causing SVC syndrome is small cell carcinoma*[Q]

**Etiologies of Superior Vena Cava Obstruction:**

| **Malignancy** | **95%** |
|---|---|
| *Lung Cancer* | *65%* |
| *Lymphoma* | *15%* |
| *Breast cancer* | *5%* |
| *Germ-cell* | *2%* |
| *Thymic cancer* | *2%* |
| *Other cancer* | *4%* |
| **Benign** | **5%** |
| *Central venous device related* | *1%* |
| *Mediastinal fibrosis* | *3%* |

- **Clinical manifestations of obstruction to SVC :**

| Symptoms | Signs |
|---|---|
| • ***Swelling around neck & face*** especially around the eyes<br>• ***Dyspnea***<br>• Cough<br>• Others: Hoarseness / Headache / Tongue Swelling / Nasal congestion / Epistaxis Haemoptysis / Dysphagia / Pain / Dizziness / Syncope | • Dilated neck veins<br>• ***Increased number of collateral veins over anterior chest wall***<br>• Cyanosis<br>• Edema of face, arms & chest<br>• Proptosis, glossal and Laryngeal edema and obtundation in severe cases |

*Symptoms are aggrevated by bending forwards and lying down.*

# Cystic Fibrosis

## Charachteristic Classical Manifestations of Cystic Fibrosis
(Typical System Involvement)

### Respiratory system (Sinopulmonary disease)

- Pulmonary infection
  Persistant colonization/infection with typical cystic fibrosis pathogens, including Staphylococcus aureus, nontypeable, Hemophilus influenzae, ***mucoid and nonmucoid Pseudomonas aeruginosa***, Burkholderia cepase
- Chronic obstructive Pulmonary Disease
- Bronchiectasis is typical
- Airway obstruction manifested by wheezing and air trapping
- Chronic cough & sputum production
- Digital clubbing
- Persistent chest radiograph abnormalities (eg. Bronchiectasis, atelectasis, infiltrates, hyperinflation)
- Nasal Polyps
  Radiographic or computed tomographic abnormalities of paranasal sinuses

### Gastrointestinal System (Intestinal; Hepatobiliary; Pancreatic)

Intestinal
meconium ileus, distal intestinal obstruction syndrome, rectal prolapse.
Pancreatic
Pancreatic exocrine deficiency
Hepatobiliary
Hepatic disease manifested by clinical or histologic evidence of focal biliary ***cirrhosis***, or multilobular ***cirrhosis***
Nutritional
Failure to thrive (protein-calorie malnutrition), hypoproteinemia, edema, complications secondary to fat-soluble vitamin deficiency

### Genitourinary System (Male Infertility)

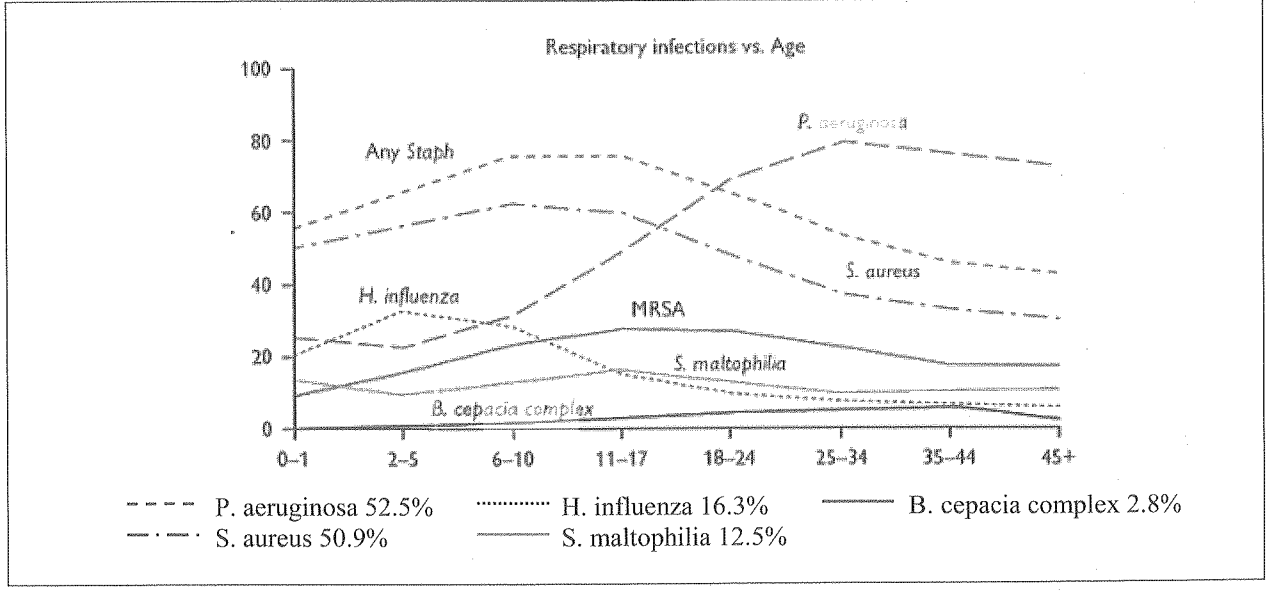
Male urogenital abnormalites resulting in obstructive zoospermia are typical

**Metabolic Abnormalities** are typically charachterized by **salt depletion syndrome**, *(Hyponatremia, Hypocholeremia and Hypokalemic Metabolic Alkalosis)*

### Pulmonary Infection in Cystic Fibrosis

- *The most common cause of Pulmonary infection in cystic fibrosis in children is staphylococcus aureus*[Q]
- *The most common cause of Pulmonary infection in cytic fibrosis in adolescents and adults is Pseudomonas Aeroginosa.*
- *The two most common cause of pulmonary infection in cystic fibrosis are staphylococcus aureus and Pseudomonas Aeroginosa*

  *Overall (all agegroups) Pseudomonas Aeroginosa is marginally more common than staphylococcus aureus as a cause of pulmonary infection in cystic fibrosis.*
- *The most* common organism causing chronic lung disease in patients with cystic fibrosis is pseudomonas aeroginosa



## Kartagener's syndrome

**Kartagener's syndrome**
*Immotile cilia syndrome*
*Primary ciliary dyskinesia*

Ultrastructural changes causing immotility of cilia

| Immotility during embryogenesis | Immotility in respiratory Epithelium | Immotility of cilia in sperms |
|---|---|---|
| *Situs inversus* [Q]<br>*Dextrocardia* [Q] | *Bronchiectasis*<br>*Situsitis*<br>Recurrent sinopulmonary infections are seen | *Infertility (male)* |

| Syndrome | Major cardiac Anomaly | Major non cardiac anomaly |
|---|---|---|
| *Kartagener's syndrome*<br>*(Immotile cilia syndrome)*<br>*(Primary ciliary dyskinesia)* | *Dextrocardia*[Q] | • *Situs inversus* [Q]<br>• *Sinusitis* [Q]<br>• *Bronchiectasis* [Q]<br>• *Infertility* [Q] |

**Note**

*Situs inversus refers to perfect mirror image of normal physiologic position of visceral organs with preservation of their A-P relationship. Situs inversus is usually associated with dextrocardia (Heart on Right Side of chest).*

## Goodpasture's Syndrome

Good pasture's syndrome

Good pasture's syndrome is an autoimmune disease characterized by formation of Anti GBM antibodies that attack both pulmonary capillaries and the Glomerulus (GBM)

*Preceding Resp infection*
*Toxic lung exposure*
*Drug exposure Etc*

*Antibodies against Non collagenous Domain (NCL) of $\alpha 3$ chain of collagen type IV (Found in Glomerular Bacement membrane & Pulmonary capillaries)*

Serology

- *Circulating Anti GBM antibodies (IgG): Positive*
- *ANCA antibodies: Typicallyy negative (May be present in upto 30% of patients)*
- *ANA antibodies : usually normal*
- *C3 levels : Usually normal*

Two Age Groups

- *Young men in late 20's (Men >> females)*
- *Men and women their 60-70's*

| Antibodies agonist Glomerular Basement Membrane (GBM) | Antibodies against pulmonary capillaries |
|---|---|
| Glomerulonephritis /Renal Disease | Pulmonary /Lung Manifestations |

- Features of Acute Glomerulonephritis (RPGN)
  - *Hematuria*[Q] - *Proteinuria*[Q]
  - Edema - *Rapidly progressive renal failure*[Q]
- Pathological Picture[Q]
  *Diffuse crescenteric Glomerulonephritis*[Q]
  *Linear IgG*[Q] *staining along basement membrane on immunofluorescence*[Q]

*Dysmorphic RBC and RBC cast are present in urine suggesting Glomerulonephritis*[Q]

Clinical

- Hemoptysis (Frank)
  *Hemoptysis is largely confined to smokers*
- Dyspnea

X-Ray finding[Q]

- *Diffuse bilateral pulmonary infiltrates*[Q]

# Cyanosis

## Cyanosis

Cyanosis is bluish discolouration of skin and mucous membrane that appears when the capillary content of reduced hemoglobin is greater than 5g/dl (Robbins, CSDT, CPDT old editions)

*According to Harrisons 17th edition cyanosis is said to become apparent when reduced Hb > 4g/dl*

### Central cyanosis

- Central cyanosis is caused by in adequate oxygenation of systemic arterial blood due to decreased arterial oxygen saturation or Hemoglobin abnormalities
- It results from cardiac shunting, pulmonary diseases or hematological disorders (Hb abnormalities)
- *Central cyanosis is charachterized by cyanosis affective both mucous membranes and skin*

Causes

**Decreased arterial oxygen saturation**

- Decreased atmospheric pressure – high altitude
- Impaired pulmonary function
  - ***Alveolar hyoventilation***
  - ***Uneven relationships between pulmonary ventilation and perfusion*** (perfusion of hypoventilated alveoli)
  - Impaired oxygen diffusion
- Anatomic shunts
  - Certain types of congenital heart disease
  - Pulmonary arteriovenous fistulas
  - Multiple small intrapulmonary shunts
- Hemoglobin with low affinity for oxygen

**Hemoglobin abnormalities**

- ***Methemoglobinemia – hereditary, acquired***
- Sulfhemoglobinema – acquired
- Carboxyhemoglobinemia (not true cyanosis)

### Peripheral cyanosis

- Peripheral cyanosis is caused by slowing of blood flow and increased extraction of oxygen from normally saturated blood
- It results from vasoconstriction or decreased peripheral blood flow, reduced cardiac output or vascular occlusion
- *Peripheral cyanosis is characterized by cyanosis of skin alone and sparing of mucous membranes*

Causes

- Vascular occlusion
  - Arterial obstruction
  - Venous obstruction
- Reduced cardiac output
- Cold exposure
- Redistribution of blood flow from extremities

# Bronchiolitis Obliterans

## Bronchiolitis Obliterans (BO)

Bronchiolitis Obliterans is a chronic lung disease that results from obstruction of bronchii, bronchioles and smaller airways from fibrous tissue.

*Obstruction by fibrous tissue may be a sequelle to: (Etiology)*

- *Respiratory infections : Most common is Adenovirus*[Q] *(Rudolph)*
- *Inhalation of toxic gases*
- *Connective tissue disorders*
- Transplant recipients[Q]

### Clinical Features

#### Initial Presentation

**Cough, fever** respiratory distress and **wheezing** followed by **initial improvement** may be the initial signs of BO –Nelson

*Presentation at this stage is similar to pneumonia, bronchitis, acute bronchiolitis*

#### Later Presentation

- **Prolonged wheeze (stridor)**
- *Chronic* **cough with sputum** *production*
- *Exercise intolerance (dyspnea)*

### Laboratory findings and imaging

*(Suggest Features of Obstructive Lung disease)*

| | | |
|---|---|---|
| *Chest X-Ray* | : | **Hyperluscency** *and Patchy infiltrates* |
| *Pulmonary* | : | **Signs of airway obstruction (obstructive curve)** |
| *V-Q scan* | : | *Typical moth eaten appearance of multiple matched defects* |

## QUESTIONS

### Respiratory failure & Disturbance in Respiratory Functions

1. False statement about type I respiratory failure is: *(AI 2001)*
   A. Decreased $PaO_2$
   B. Decreased $PaCO_2$
   C. Normal $PaCO_2$
   D. Normal A-a gradient
2. In type - II respiratory failure, there is : *(AIIMS Nov 02)*
   A. Low pO2 and low $pCO_2$
   B. Low pO2 and high $pCO_2$
   C. Normal pO2 and high $pCO_2$.
   D. Low pO2 and normal $pCO_2$.
3. A patient with salicylic acid poisoning has the following arterial blood gas analysis report : pH = 7.12 : $pCO_2$ = 18mmHg; $HCO_3$ = 12mmol/L. The resulting acid base abnormality can be best labeled as: *(AIIMS Nov 03)*
   A. Metabolic acidosis with compensatory respiratory alkalosis
   B. Metabolic acidosis with compensatory respiratory alkalosis
   C. Respiratory acidosis with metabolic alkalosis
   D. Metabolic acidosis
4. In a patient $PO_2$ is 85 mmHg, $PCO_2$ – 50mmHg, pH is 7.2 and $HCO_3$ is 32 meq/l is suffering from :
   A. Respiratory acidosis with compensatory metabolic alkalosis *(AIIMS June 2000)*
   B. Respiratory acidosis with compensatory metabolic acidosis
   C. Metabolic acidosis
   D. Metabolic alkalosis
5. A patient presents with following parameters pH 7.5, p $CO_2$ 30 mmHg, $pO_2$ 102 mmHg and $HCO_3$ 16 meq/l. Which of the following correctly describes the compensatory mechanism: *(AI 2010)*
   A. Respiratory Alkalosis
   B. Metabolic Alkalosis
   C. Respiratory Acidosis
   D. Metabolic Acidosis
6. The acid base status of a patient reveals a $p^H$ = 7.46 and $pCO_2$=30 mm Hg. The patient has a partially compensated primary: *(AI 2011)*
   A. Metabolic acidosis
   B. Metabolic alkalosis
   C. Respiratory alkalosis
   D. Respiratory acidosis
7. A patient was admited to the casualty with hysteria and anxiety. Estimation of arterial plasma showed PH of 7.53; $HCO_3$ of 22 meq and $Pco_2$ of 27 mm H g. which of the following is the patient likely to have?
   A. Metabolic acidosis *(NBE)*
   B. Metabolic alkalosis
   C. Respiratory acidosis
   D. Respiratory alkalosis
8. Arterial blood gas analysis of a patient reveals pH 7.2, $HCO_3$ 36mmol/L, $pCO_2$ 60mm of Hg. The abnormality is : *(AIIMS June 99)*
   A. Respiratory acidosis with compensatory metabolic alkalosis *(AI 1996)*
   B. Respiratory acidosis
   C. Respiratory alkalosis with compensatory metabolic acidosis
   D. Respiratory acidosis with compensatory metabolic acidosis
9. A 40 year old male develops excessive hyperventilation. ABG reveals pH- 7.5, $PCO_2$ 24 mmHg, $PO_2$ 88 mm of Hg. Treatment is :
   A. Respiratory alkalosis *(AIIMS June 1999)*
   B. Metabolic alkalosis
   C. Respiratory acidosis
   D. Metabolic acidosis
10. An ABG analysis shows : pH 7.2, raised $pCO_2$, decreased $HCO_3$; diagnosis is : *(AIIMS June 97)*
    A. Respiratory acidosis
    B. Compensated metabolic acidosis
    C. Respiratory and metabolic acidosis
    D. Respiratory alkalosis
11. A 10 year old boy with short stature presents with polyuria & polydipsia. Laboratory values reveal a pH of 7.4; $HCO^3$ of 17; $Na^+$ 140; pCO2 32; $K^+$ 4.9; $Cl^-$ 112. Likely acid base abnormality is:
    A. Metabolic Alkalosis *(AIIMS Nov 2010)*
    B. Non-Anion gap Metabolic Acidosis
    C. Anion gap Metabolic Acidosis
    D. Respiratory Acidosis
12. Blood gas measurements of a patient shows the following values pH 7.2, pCO2 80 mm Hg, pO2 46 mm Hg. Which of the following could be the most probable diagnosis: *(AIIMS Nov 2000)*
    A. Acute asthma
    B. Acute exacerbation of COPD
    C. ARDS
    D. Severe pneumonia
13. The blood gas parameters: pH 7.58, pC02 23 mm Hg pO2 300 mm Hg and oxygen saturation 60% are most consistent with- *(AI 03)*
    A. Carbon monoxide poisoning
    B. Ventilatory malfunction
    C. Voluntary hyperventilation
    D. Methyl alcohol poisoning

## Obstructive / Restrictive Pulmonary Diseases

### Pulmonary Function Test

14. All the following are true about Chronic Obstructive lung disease *except:*
    A. Decreased $FeV_1$ *(AI 1994)*
    B. Decreased MEFR *(AIIMS June 97)*
    C. Increased RV
    D. Decreased diffusion capacity

15. All of the following are characteristic feature of obstructive pulmonary disease, except:
    A. Normal Residual Volume *(NBE)*
    B. Decreased $FEV_1$
    C. Normal Vital Capacity
    D. Decreased $FCV_1/FVC$

16. $FEV_1/FVC$ is reduced in case of :
    A. Pleural effusion *(AIIMS May 95)*
    B. Lung fibrosis
    C. Asthma
    D. All of the above

17. FEVI/FVC is decreased in: *(NBE)*
    A. Asthma
    B. Kyphosis
    C. Scoliosis
    D. Fibrosis

18. Pulmonary function changes in acute bronchial asthma in untreated patient - *(PGI June 03)*
    A. ↑ ed peak expiratory flow
    B. ↓ ed TLC
    C. ↑ ed FVC
    D. ↑ ed RV
    E. ↑ ed FEV

19. Features of restrictive lung disease is *(AIIMS June 98)*
    A. $FEV_1/FVC$ decreases and compliance decreases
    B. $FEV_1/FVC$ increases and compliance increases
    C. $FEV_1/FVC$ decreases and compliance increases
    D. $FEV_1/FVC$ increases and compliance decreases

20. The abnormal preoperative pulmonary function test in a patient with severe kyphoscoliosis includes:
    A. Reduced RV/TLC *(AI 05)*
    B. Reduced FEV1/FVC.
    C. Reduced FEV25-75
    D. Increased FRC

21. A 28 years old woman having limited cutaneous scleroderma for the last 10 years comaplins of shortness of breath for last one month. Her pulmonary functions tests (PFT) are as follows :

| PFT | Observed | Predicted |
|---|---|---|
| FVC | 2.63 | 2.82 |
| $FEV_{1\%}$ | 88% | 80% |
| DLCO | 5.26 | 16.3 |

What is the most likely diagnosis in this case ?
    A. Intestitial lung disease *(AI 06)*
    B. Pulmonary artery hypertension
    C. Congestive heart failure
    D. Bronchiectasis

22. A 28 years old woman having limited cutaneous scleroderma for the last 10 years complains of shortness of breath for last one month. Her pulmonary functions tests (PFT) are as follows:

| PFT | Observed | Predicted |
|---|---|---|
| FVC | 2.63 | 2.82 |
| $FEV_1^{\%}$ | 88% | 80% |
| DLCO | 5.26 | 16.3 |

What is the most likely diagnosis in this case?
    A. Interstitial lung disease *(AIIMS Nov 09)*
    B. Pulmonary artery hypertension
    C. Congestive heart failure
    D. Bronchiectasis

23. A patient presents with decreased vital capacity and total lung volume. What is the most probable diagnosis? *(AI 2007)*
    A. Bronchiectasis
    B. Sarcoidosis
    C. Cystic fibrosis
    D. Asthma

24. All are decreased in infiltrative lung disease, *except*:
    A. Vital capacity *(AIIMS Feb 97)*
    B. Alveolar arterial difference in $PaO_2$
    C. Total lung capacity
    D. Lung compliance

25. Carbon monoxide diffusion capacity decreases in all, *except* : *(AIIMS Feb 97) (AI-2003)*
    A. Emphysema
    B. Primary pulmonary hypertension
    C. Alveolar haemorrhage
    D. Infiltrative lung disease

26. Diffusion capacity for carbon monoxide is decreased in all of the following Except: *(AIIMS May 94)*
    A. Chronic Bronchitis
    B. Emphysema
    C. Interstitial lung disease
    D. Pulmonary embolism

27. Decreased maximum mid-expiratory flow rate indicates obstruction in : *(AI 1994)*
    A. Small airways *(AIIMS May 95)*
    B. Trachea
    C. Large airways
    D. Trachea & Bronchi both

### Bronchial Asthma

28. All of the following are true about intrinsic Asthma, Except: *(PGI Dec 04)*
    A. Increasing Incidence
    B. Allergic Asthma is more common in young patients

C. Idiosyncratic Asthma is more common older patients
D. IgE is increased in Idiosyncratic Asthma
E. IgE is increased in Extrinsic Asthma

29. All of the following statements about intrinsic allergic Asthma are true, Except: *(PGI 2009)*
A. Nasal polyp
B. Normal IgE
C. Family history Positive
D. More aggressive
E. Allergic in nature

30. Asprin sensitive asthma is associated with which of the following? *(NBE)*
A. Obesity
B. Urticarla
C. Nasal polyp
D. Extrinsic asthma

31. Aspirin-sensitive asthma is associated with:
A. Obesity *(AI 1995)*
B. Urticaria
C. Nasal polyp
D. Extrinsic asthma

32. Bronchial Asthma is characterized by all of the following, Except: *(PGI June 05)*
A. Inflammatory disease of airway
B. Allergic disease of airway
C. Hyporesponsive ness of airway
D. Hyperresponsiveness of airway
E. Treatment is mostly inhaled steroid

33. All of the following are true about Asthma, Except:
A. Charcol Leydin crystals may be seen in sputum
B. Reversible Airflow obstruction is a characteristic feature *(NBE)*
C. Large airways are involved
D. Small airways are not involved
E. Intermittent Asthma responds better to bronchodilator therapy than persistant Asthma

34. True about Asthma except: *(PGI 05)*
A. Inflammatory disease
B. Hyperresponsive airways
C. Necrosis of airways
D. Mucous plug formation
E. Airway edema

35. Feature of Acute severe Asthma include all of the following, Except: *(NBE)*
A. Tachycardia > 120/min
B. Pulsus paradoxus
C. Respiratory acidosis
D. PEFR < 50%
E. None (All are Features of Acute severe Asthma)

36. In a patient with bronchial asthma silent chest signifies *(NBE)*
A. Good Prognosis
B. Bad Prognosis
C. Grave Prognosis
D. Not a Prognostic sign

37. An Adult with asthma presents with asthma symptoms every day and wakes up in the night approximately 2 to 3 days in a week. He can be classified as having : *(NBE)*
A. Intermittent Asthma
B. Mild Persistent Asthma
C. Moderate Persistent Asthma
D. Severe Persistent Asthma

38. Universal finding in Asthma is *(PGI June 02)*
A. Hypoxia
B. Hypercarbia
C. Respiratory acidosis
D. Metabolic Acidosis

39. In a Patient with clinical signs of Asthma which of the following tests will confirm the diagnosis: *(NBE)*
A. Increase in FEV1/FVC
B. > 200 ml increase in FEV1 after Methacholine
C. Diurnal variation in PEF > 20 Percent
D. Reduction of FEV1 > 20 % after bronchodilators

40. A Patient with history of shortness of breath has Decreased FEV1/FVC Ratio, Normal DLCO. A 200 ml increase in baseline FEV1 is observed 15 minutes after administration of bronchodilators. The likely diagnosis is: *(NBE)*
A. Asthma
B. Chronic Bronchitis
C. Emphysema
D. Interstitial Lung Disease

41. Bronchial Asthma is best diagnosed by: *(PGI Dec 01)*
A. Wheeze
B. Dyspnea and cough
C. $FEV_1$ values
D. Demonstration of Reversible obstruction
E. Normal $FEV_1$

42. Anti-inflammatory action on airways is seen with (Mark two correct option): *(PGI June 05)*
A. Fluticasone
B. Iprotropium bromide
C. Budesonide
D. Theophylline
E. Tebutaline

43. All are used in bronchial asthma, *except* :
A. Salbutamol *(AIIMS June 97)*
B. Morphine
C. Aminophylline
D. Steroid

44. All of the following are used in Bronchial Asthma, Except: *(NBE)*
A. Salbutamol
B. Aminophylline
C. Steroids
D. Morphine

45. All of the following drugs useful in the treatment of a patient with acute bronchial asthma *except :*

A. Ipratropium *(AIIMS Nov 03)*
B. Salbutamol
C. Montelukast
D. Hydrocortisone

46. All of the following statements about Leukotriene modifiers in the management of bronchial asthma are true except : *(AIIMS May 1996)*
A. May be used for acute asthma
B. May be used for exercise induced asthma
C. Zileuton is Leukotriene modifier
D. May uncover Churg strauss syndrome

47. Antibody used in the treatment of Bronchial Asthma is: *(NBE)*
A. Omalizumab
B. Rituximab
C. Daclizumab
D. Transtusuzumab

48. The most predictive and dangerous side effect of propranolol that makes it to be avoided in known patient of COPD is induction of : *(AIIMS Nov 01)*
A. Respiratory failure
B. Acute asthmatic attack
C. Glaucoma
D. Pleural effusion

49. A drug is to be delivered by a nebuliser. The size of a droplet for its humidification is :
A. $< 5\ \mu$ *(AI 2000)*
B. 5-10
C. 10-15
D. 15-20

## Chronic Bronchitis

50. Increased Reid Index is used to characterized:
A. Chronic Bronchitis *(AI 2012)*
B. Bronchiectasis
C. Bronchial Asthma
D. Emphysema

51. Which of the following is the least common bacteria responsible for Acute Exacerbation of Chronic Bronchitis *(NBE)*
A. Streptococcus pneumoniae
B. Moraxella catarrhalis
C. Haemophilus influenza
D. Staphylocccus aureus

## Emphysema

52. $\alpha_1$ Antitrypsin deficiency is associated with :
A. Centriaciner emphysema *(AI 1999)*
B. Panaciner-emphysema
C. Irregular emphysema
D. Paraseptal-emphysema

53. All of the following statements about Emphysema are true, Except: *(PGI Dec 04)*
A. Breathlessness is the charachteristic presenting symptom
B. Diffusion rate of carbon monoxide is reduced
C. Restrictive pattern on pulmonary function test is seen
D. Long term bronchadilater therapy does not improve lung function

54. Lung functions in Emphysema reveal all of the following , Except *(PGI – Dec –01)*
A. Decreased vital capacity
B. Increased diffusion capacity for carbon monoxide (DLCO)
C. Increased Total Lung capacity
D. Decreased $FEV_1$
E. Decreased $FEV_1$ / FVC ratio

55. In an emphysematous patient with bullous lesions, which is the best investigation to measure lung volume: *(AIIMS Nov 08)*
A. Body Plethysmography
B. Gas dilution
C. Transdiaphragmatic pressure
D. DLco

## Bronchiectasis

56. Bilateral upper lobe bronchiectasis suggests a diagnosis of: *(NBE)*
A. Tuberculosis
B. Cystic Fibrosis
C. Rheumatoid Arthritis
D. Recurrent Aspiration

57. Bronchiectasis is most common in which lobe:
A. Right upper lobe *(AIIMS May 95)*
B. Right middle lobe
C. Left upper lobe
D. Left lower lobe

58. Bronchiectasis Sicca is seen with:
A. Tuberculosis *(NBE)*
B. Pertussis
C. Cystic fibrosis
D. Kartagener syndrome

59. Brock's Syndrome is: *(NBE)*
A. Bronchiectasis Sicca
B. Middle Lobe Bronchiectasis
C. Kartagener's Syndrome
D. Sarcoidosis

60. Which of the following is NOT a complication of bronchiectasis : *(AIIMS Sept 96) (AI 1998)*
A. Lung abscess
B. Lung cancer
C. Amylodosis
D. Empyema

61. Rampal, 45 yr old man presents with history of recurrent hemoptysis and purulent sputum. His chest X-Ray is normal, which of the following will be the next best investigation for him? *(AIIMS Nov 01)*

A. HRCT
B. CT guided angiography
C. Angiography
D. Spiral CT

## Interstitial Lung Disease

62. All are true about Interstitial Fibrosis, Except
A. FVC < 80% Predicted
B. FEV1/FVC < 0.7 *(PGI – June 03)*
C. DLCO is decreased
D. TLC is decreased

63. All of the following are true about interstitial lung disease, Except: *(PGI June 07)*
A. Decreased FVC
B. Decreased FEV1
C. Decreased FEV1/FVC
D. Decreased Diffusion capacity

64. A 40 year old female presents with progressive dyspnea for one year. Physical examination reveals bibasilar end-inspiratory crepitations. All of the following statements about her condition are true, Except: *(NBE)*
A. May be associated with connective tissue disease
B. Residual volume is increased
C. Total Lung capacity is decreased
D. HRCT is a useful diagnostic test

65. A female presents with history of progressive breathlessness. Histology shows heterogenous patchy fibrosis with several fibroblastic foci. The most likely diagnosis is: *(AI 2010)*
A. Cryptogenic Organizing Pneumonia
B. Non Specific Interstitial pneumonia
C. Usual Interstitial Pneumonia
D. Desquamative Interstitial Pneumonia

66. Investigation of choice for interstitial disease is:
A. Chest X-ray *(AIPGMEE 08)*
B. HRCT
C. Gallium-67 DTPA scan
D. MRI

67. Investigation of choice for detection and characterization of interstitial lung disease is:
A. MRI. *(NBE)*
B. Chest x-ray.
C. High resolution CT.
D. Ventilation perfusion scan.

68. Farmer's Lung is caused due to exposure to: *(NBE)*
A. Bacillus Subtilis
B. Thermoactinomyces Sacchari
C. Aspergillus Fumigatus
D. Penicillium Nalgiovens

69. Farmer's lung is caused due to exposure to: *(NBE)*
A. Bacillus subtilis
B. Thermoactinomyces saccharri
C. Aspergillus fumigates
D. Penicillium nalgiovense

70. Occupational Lung Disease commonly seen in Textile Industry Workers is: *(NBE)*
A. Byssinosis
B. Bagassosis
C. Farmer's Lung
D. Asbestosis

71. Which of the following is characteristically not associated with the development of interstitial lung disease? *(AI 2002)*
A. Coal dust
B. Sulfur dioxide
C. Thermophilic actenomycetes
D. Tobacco smokes

72. Caplan Syndrome is Pneumoconiosis with
A. Lymphadenopathy
B. Congestive Cardiac Failure
C. Rheumatoid Arthritis
D. HIV

73. All of the following features are seen in asbestosis except- *(AIIMS Nov 02)*
A. Diffuse pulmonary interstitial fibrosis
B. Fibrous pleural thickening
C. Emphysema
D. Calcific pleural plaques

74. True statements about asbestosis – *(PGI Dec 04)*
A. Causes Lung Ca
B. Pleural mesothelioma
C. Peritoneal mesothelioma
D. Pulmonary fibrosis
E. All of the above

75. All of the following statements about silicosis are true, Except *(PGI Dec 04)*
A. Pleural plaques
B. Prediliction for upper lobes
C. Calcific Hilar Lymphadenopathy
D. Associated with tuberculosis

76. Which of the following is true about pneumoconiosis
A. Pleural plaques of asbestosis is always symptomatic *(NBE)*
B. Silicosis is not associated with increased risk of Tuberculosis
C. Asbestosis and smoking act synergistically to cause lung cancer
D. Coal Workers Pneumoconiosis is associated with Lung cancer

77. Not seen idiopathic pulmonary hemosiderosis
A. Eosinopenia *(AI 2009)*
B. Iron deficiency anemia
C. Diffuse alveolar hemorrhage
D. Hemoptysis

78. All of the following are true about Idiopathic Pulmonary Hemosiderosis Except:
A. Hypoxemia
B. Alveolar capillary constriction
C. Hyperplasia of type II Pneumocytes
D. Hemosiderin laden macrophages

79. All of the following are associated with pulmonary eosinophillic pneumonia, Except: *(PGI 2009)*
A. ABPA
B. Loeffler's pneumonia
C. Churg Strauss Syndrome
D. Tropical pulmonary eosinophilia
E. Wegener's granulomatosis

80. Lower lobe fibrosis is seen in : *(NBE)*
A. Silicosis
B. Sarcoidosis
C. Cystic Fibrosis
D. Asbestosis

## Allergic Bronchopulmonary Aspergillosis (ABPA)

81. Diagnostic features of allergic bronchopulmonary aspergillosis (ABPA) include all of the following *except*: *(AI 2003)*
A. Changing pulmonary infiltrates
B. Peripheral eosinophilia
C. Serum precipitins against Aspergillosis fumigants
D. Occurrence in patients with old cavitatory lesions.

82. Diagnostic criteria for Allergic Bronchopulmonary Aspergillosis include all, except *(PGI-Dec05)*
A. Peripheral eosinophilia ($>0.1 \times 10^9/mm^3$)
B. Central bronchiectasis
C. Episodic Asthma
D. Detection of Aspergillus in sputum
E. ↑ IgG antibodies specific to A. Fumigatus

83. A 40 year old man presented with repeated episodes of bronchospasm and hemoptysis. Chest X-ray revealed perihilar bronchiectasis. The most likely diagnosis is : *(AI 2002)*
A. Sarcoidosis
B. Idiopathic pulmonary fibrosis
C. Extrinsic allergic alveolitis
D. Bronchopulmonary aspergillosis

84. All the following are true about bronchopulmonary aspergillosis *except*: *(AI 1995)*
A. Central bronchiectasis
B. Pleural effusion
C. Asthma
D. Eosinophilia

85. True statements about ABPA include all of the following, Except: *(PGI Dec 04)*
A. Serum IgE > 1000 ng/ml
B. Eosinophils > $1000/mm^3$
C. Elevated IgG antibodies
D. Proximal Bronchiectasis
E. Lower lobe predominance

86. Which is not true about aspergillosis- *(NBE)*
A. Aspergillus Niger is the cause of fungal otitis externa
B. It is highly contagious
C. Aspergilloma is common in preexisting TB, or cystic disease
D. Aspergillus fumigatus is a cause of bronchial aspergillosis

87. 40 year old patient with history of prolonged exposure to Aspergillus presents with repeated episodes of breathlessness. Chest X-ray shows diffuse pulmonary infiltrates. Skin hypersensitivity test is positive for Aspergillus antigen Peripheral blood picture shows normal eosinophil count and serum IgE levels are normal The most likely diagnosis is *(NBE)*
A. Allergic bronchial Asthma
B. Allergic Bronchopulmonary Aspergillosis (ABPA)
C. Extrinsic Allergic Alveolitis
D. Invasive Pulmonary Aspergillosis

88. All the following are features of Tropical pulmonary Eosinophilia except- *(NBE)*
A. Eosinophilia > 3000/mm3
B. Microfilaria in blood
C. Paroxysmal cough and wheeze
D. Bilateral chest mottling and increased bronchovascular markings

89. Tropical pulmonary eosinophilia is caused because of: *(NBE)*
A. Occult filariasis.
B. Cerebral malaria.
C. Pneumonic plsgue.
D. Asthmatic bronchitis.

90. All the following diseases are associated with peripheral blood eosinophilia *except* :
A. Allergic bronchopulmonary aspergillosis (ABPA). *(AIIMS Nov 02)*
B. Loffler's syndrome.
C. Pulmonary eosinophilic granuloma.
D. Chrug-Strauss syndrome.

91. A 54 year old smoker man comes with severe hemoptysis weight loss and oligoarthritis. Serial skiagram shows fleeting opacities. What is the diagnosis? *(AIIMS Nov 08)*
A. Allergic bronchopulmonary aspergillosis
B. Ca lung
C. Tb
D. Wegener's granulomatosis

# Pneumonias and Tuberculosis

## Bacterial Pneumonia

92. Most common pattern of Pneumonia seen in Klebsiella infection is: *(NBE)*
A. Lobar Pneumonia
B. Bronchopneumonia
C. Interstitial Pneumonia
D. Miliary Pneumonia

93. All of the following statements about Pneumococcal Pneumonia are true, except : *(NBE)*
    A. Non-segmental Consolidation
    B. Air Bronchogram Absent
    C. Usually confined to one lobe
    D. Cavitation is rare
94. All of the following are more commonly seen in Klebsiella Pneumonia than in Pneumococcal Pneumonia, Except: *(NBE)*
    A. Lower lobe involvement
    B. Abscess Formation
    C. Pleural Effusion
    D. Cavitation
95. Friedlander Pneumonia refers to Pneumonia caused by: *(NBE)*
    A. Klebsiella
    B. Pneumococcus
    C. H. Influenzae
    D. Staphylococcus
96. The most common causative organism for lobar pneumonia is: *(NBE)*
    A. Staphylococcus aureus
    B. Streptococcus pyogenes
    C. Streptococcus pheumoniae
    D. Haemophilus influenza
97. Round pneumonia is seen with: *(NBE)*
    A. Streptococcal pneumonia
    B. Kerosene oil aspiration
    C. Lung cancer
    D. Mendelson syndrome
98. Nosocomial pneumonia is most commonly caused by:
    A. Gram -ve bacilli *(AI 1998)*
    B. Gram +ve bacilli
    C. Gram -ve cocci
    D. Mycoplasma
99. Predisposing factors for Pneumococcal Pneumonia include all of the following Except: *(PGI June 01)*
    A. CRF
    B. Lymphoma
    C. Old Age
    D. Thalassemia
    E. Sickle cell disease
100. Cavitatory lesions in lung are seen in: *(AI 2010)*
    A. Primary pulmonary Tuberculosis
    B. Staphylococcal pneumonia
    C. Preumoconiosis
    D. Interstitial Lung disease
101. Devi, a 28 year female, has diarrhoea, confusion, high grade fever with bilateral pneumonitis. The diagnosis is : *(AI 2000)*
    A. Legionella
    B. Neisseria meningitis
    C. Streptococcus pneumoniae
    D. H. influenza
102. A 30 year old male presents with pneumonia and diarrhea five days after discharge from a hospital. The drug of choice for treating him is: *(NBE)*
    A. Vancomycin
    B. Ciprofloxacin
    C. Azithromycin
    D. Gentamycin
    E. Tetracycline
103. An elderly male admitted for Pneumonia presents with diarrhea and gripping abdominal pain five days after discharge from the hospital. Drug which is likely to benefit is. *(NBE)*
    A. Imodium
    B. Metranidozole
    C. Diphenoxylate
    D. Levofloxacin
104. Which is not true about legionnaire pneumonia:
    A. Seen mainly in immunocompromised person
    B. Erythromycin is drug of choice *(AIIMS May 95)*
    C. Common in patients with hairy cell leukemia
    D. Smoking and alcohol are risk factor.
105. Fever persisting even after treatment of pneumonia likely diagnosis is : *(AIIMS June 97)*
    A. Empyema
    B. Fungal lesion
    C. Carcinoma bronchus
    D. Any of the above
106. Most common cause of empyema is:
    A. Bronchopleural fistula *(AIIMS Dec 97)*
    B. Tubercular pneumonia
    C. Bacterial pneumonia
    D. Pleurisy

## Atypical Pneumonia

107. Atypical pneumonia can be caused by the following microbial agents *except*? *(AI 2005)*
    A. Mycoplasma pneumoniae.
    B. Legionella pemmophila.
    C. Human Corona virus.
    D. Klebsiella pneumoniae.
108. All of the following features are seen in the viral pneumonia *except* : *(AI 2005)*
    A. Presence of interstitial inflammation.
    B. Predominance of alveolar exudates.
    C. Bronchiolitis.
    D. Multinucleate giant cells in the bronchiolar wall.
109. Features of pneumocystic carini pneumonia are:
    A. Interstial pneumonitis *(PGI Dec 98)*
    B. Eosinophilic exudate
    C. Damage to type I pneumocytes
    D. Hypertrophy of type II pneumocytes
    E. All of the above
110. A 45 year old, HIV positive patient presents with features of pneumonia. Characteristic histopathological features suggesting pneumocystis carinii pneumonia is: *(PGI-Dec-2000)*
    A. Prominent Interstitial Pneumonitis
    B. Eosinophilic Alveolar Exudates

C. Prominent mononuclear cells in Alveolar exudates
D. Neutrophilic infiltration of alveolar interstitium
E. Hypertrophy of type I pneumocytes

111. A truck driver presented with history of fever since four weeks, and dry cough. He also gives a history of weight loss of about 10 kg. X-ray shows bilateral reticulonodular infiltrates. The most likely diagnosis is: *(AI 2010)*
A. Tuberculosis
B. Pneumocystis carinii Pneumonia
C. Pneumococcal pneumonia
D. Interstitial Lung Disease

112. All of the following statements about Pneumocystis Jiroveci are true Except: *(AI 2008)*
A. Usually associated with CMV infection
B. May be associated with Pneumatocele
C. Usually diagnosed by sputum examination
D. Causes disease only in the immunocompromised host

113. True Statement about Pneumocystic Jiroveci is: *(NBE)*
A. Often associated with CMV infection
B. Usually diagnosed by sputum examination
C. Infection occurs only in immunocompromised patients
D. Always associated with Pneumatocele

114. Indication for prophylaxis in pneumocystis carini pneumonia include (choose two best option) *(NBE)*
A. $CD_4$ count < 200 /µl
B. Tuberculosis
C. Viral load > 25,000 copies/ml
D. Oral candidiasis

115. All the following are used in the treatment of *Pneumocystis carinii except:* *(AI 1994)*
A. Pentamidine
B. Dapsone
C. Cotrimoxazole
D. Fluoroquinolones

116. Drug of choice for pneumocystis carinii is: *(NBE)*
A. Doxycycline
B. Cotrimoxazole
C. Tetracycline
D. Dapsone

117. Drug of choice for *Mycoplasma pneumoniae* is :
A. Penicillin *(AIIMS Dec 94, May 94)*
B. Tetracycline
C. Cefuroxime
D. Erythromycin

118. In mycoplasma pneumonia, following are seen except
A. Diffuse infiltration of lungs *(PGI-Dec-97)*
B. Cannot be cultured routinely
C. Cefotaxime is the drug of choice
D. Serology is useful in diagnosis

119. Treatment of chlamydia pneumonia is :
A. Erythromycin *(AIIMS Sept 96)*
B. Ceftriaxone
C. Penicillin
D. Sulphonamide

120. Commonest sign of aspiration pneumonitis is :
A. Cyanosis *(AIIMS Dec 94)*
B. Tachypnea
C. Crepitations
D. Rhonchi

## Tuberculosis

121. True regarding presentation of primary T.B. is :
A. B/L pleural effusion with negative Tuberculin test. *(AIIMS Dec 98)*
B. U/L hilar lymphadenopathy
C. Sustained chronic pyrexia
D. B/L pleural effusion with positive tuberculin test.

122. All of the following statements about primary Tuberculosis are true, Except: *(NBE)*
A. Cavitatory lesion
B. Pleural effusion
C. Fibrocasseous lesion
D. Phlyctenular conjunctivitis

123. All are features of primary tuberculosis; *except* :
A. Pleural effusion *(AIIMS June 98)*
B. Consolidation
C. Pulmonary fibrosis
D. Lymphadenopathy

124. Primary Tuberculosis most commonly involves
A. Lungs *(NBE)*
B. Liver
C. Brain
D. Intestine

125. Primary complex in which of the following sites suggest congenital tuberculosis *(NBE)*
A. Lungs
B. Liver
C. Lymph nodes
D. Skin

126. Most common site of primary infection in congenital tuberculosis is *(NBE)*
A. Lungs
B. Liver
C. Lymph nodes
D. Skin

127. Primary complex in Liver in Congenital tuberculosis occurs through *(NBE)*
A. Lymphatic Spread
B. Haematogenous Spread
C. Aspiration of Infected Amniotic fluid
D. Ingestion of Infected Amniotic Fluid

128. Most commonly involved organ in congenital tuberculosis is *(NBE)*
A. Lungs
B. Liver
C. Lymph nodes
D. Skin

129. All of the following statements about Miliary Tuberculosis are true Except: *(NBE)*
   A. May occur following primary infection
   B. May occur following secondary reactivation
   C. Sputum microscopy is usually negative
   D. Montoux is always positive
   E. Liver, kidney and spleen are common sites of involvement

130. The following statement stands *true* for Mantoux test
   A. Test is read before 48 hrs *(AI 1996)*
   B. 6-9 mm induration shows maximum chances of developing TB
   C. A positive test does not indicate that the person is suffering from disease.
   D. New cases are more likely to occur in tuberculin negative person than those who already are tuberculin reactors

131. False-negative tuberculin test is seen in *all except:*
   A. After 4-6 weeks of measles attack *(AI 1996)*
   B. Immunodeficiency state
   C. Miliary tuberculosis
   D. Atypical mycobacterial infection

132. Investigations in a clinically suspected case of tuberculosis – *(PGI June 07)*
   A. Mantoux (in children)
   B. Sputum AFB
   C. PCR
   D. Bactec
   E. All of the above

133. A man presents with fever, wt loss and cough; Mantoux reads an induration of 17 x 19 mm; Sputum cytology is negative for AFB. Most likely diagnosis is: *AI 2001)*
   A. Pulm tuberculosis
   B. Fungal infection
   C. Viral infection
   D. Pneumonia

134. A 25 year old man presented with fever, cough, expectoration and breathlessness of 2 months duration. Contrast enhanced computed tomography of the chest showed bilateral upper lobe fibrotic lesions and mediastinum had enlarged necrotic nodes with peripheral rim enhancement. Which one of the following is the most probable diagnosis: *(AI 03)*
   A. Sarcoidosis
   B. Tuberculosis
   C. Lymphoma
   D. Silicosis

135. A 25 year old man presented with fever and cough, expectoration and breathlessness of 2 months duration. Contrast enhanced computed tomography of the chest showed bilateral upper lobe fibrotic lesions and mediastinum had enlarged necrotic nodes with peripheral rim enhancement. Which one of the following is the most probable diagnosis:
   A. Sarcoidosis *(AIIMS May 04)*
   B. Tuberculosis
   C. Lymphoma
   D. Silicosis

136. Rasmussen's aneurysm arises from *(NBE)*
   A. Bronchial artery
   B. Pulmonary artery
   C. Vertebral artery
   D. Posterior intercostals artery

137. Multidrug Resistance Tuberculosis (MDR-TB) should be considered in patients with:
   A. Contact with a known case of MDR TB
   B. Clinical Deterioration *(PGI-Dec-05)*
   C. Sputum smear positive at 5 months of treatment
   D. All of the above

138. Multi drug resistant tuberculosis is defined as resistance to? *(NBE)*
   A. INH and Pyrizinamide
   B. INH and Rifampicin
   C. Rifampicin and Pyrizinamide
   D. Resistance to all first line drugs

139. A young man with tuberculosis presents with massive recurrent hemoptysis. For angiographic treatment which vascular structure should be evaluated first-
   A. Pulmonary artery *(AIIMS May 03)*
   B. Bronchial artery
   C. Pulomary vein
   D. Superior vena cava

## Sarcoidosis

140. B/L hilar lymphadenopathy, along with non caseating granulomas is a characteristic feature of: *(AI 1997)*
   A. Sarcoidosis
   B. Scleroderma
   C. SLE
   D. Stein-leventhal syndrome

141. All are correct regarding sarcoidosis *except* :
   A. Often cavitate *(AIIMS Dec 98)*
   B. Spontancous remission is usual
   C. Tuberculine test is negative
   D. B/L hilar lymphadenopathy.

142. Which is the most common organ involved in Sarcoidosis: *(NBE)*
   A. Lung
   B. Liver
   C. CNS
   D. Eye

143. A woman is admitted with complains of low-grade fever of 6 weeks duration. Chest radiograph reveals bihilar adenopathy with clear lung fields. All of the following investigations will be useful in differential diagnosis *except* : *(AI 2004)*
   A. CD4/CD8 counts in the blood
   B. Serum ACE levels
   C. CECT of chest
   D. Gallium scan

144. Kviem Siltzbach test is used in the diagnosis of:
A. Tuberculosis *(NBE)*
B. Sarcoidosis
C. Histoplasmosis
D. Leishmaniasis

145. Lambda -Panda sign is typically seen in:
A. Sarcoidosis *(NBE)*
B. Tuberculosis
C. Histoplasmosis
D. Leishmaniasis

146. Garland sign on CXR in sarcoidosis involves all except: *(NBE)*
A. Right paratracheal nodes
B. Right hilar nodes
C. Left hilar nodes
D. Left pretracheal lymph nodes

147. Treatment Of choice in acute Sarcoidosis is:
A. Prednisolone *(NBE)*
B. Cyclosporin
C. Infliximab
D. IV Immunoglobulins

## Pulmonary Edema

148. Hydrostatic Pulmonary edema with fluid in alveoli is usually seen when PCWP is: *(NBE)*
A. >6 mm Hg
B. >10 mm Hg
C. >15 mm Hg
D. >25 mm Hg

149. Normal Pulmonary Capillary Wedge Pressure (PCWP) is: *(NBE)*
A. 6-12 mm Hg
B. 10-14 mm Hg
C. 12-18 mm Hg
D. 18-25 mm Hg

150. Severe pulmonary edema is seen when PCWP rises above? *(NBE)*
A. 5 mm Hg
B. 10 mm Hg
C. 15 mm Hg
D. 25 mm Hg

## Adult Respiratory Distress Syndrome (ARDS)

151. Shock Lung is better known as: *(NBE)*
A. Alveolar Proteinosis
B. Alveolar Haemorrhage
C. Pulmonary edema
D. ARDS

152. Shock lung is characterized by which of the following? *(NBE)*
A. Alveolar proteinosis
B. Bronchiolitis obliterans
C. Diffuse alveolar damage
D. Diffuse pulmonary hemorrhage

153. Acute lung injury in caused by all of the following *except :* *(AIIMS May 02)*
A. Aspiration
B. Toxic gas inhalation
C. Cardiopulmonary bypass with heart lung machine.
D. Lung contusion.

154. Normal PCWP with pulmonary oedema is seen in :
A. Left atrial myxoma *(AIIMS June 98)*
B. High altitude
C. Pulmonary vein obstruction
D. Pulmonary artery obstruction.

155. Normal PCWP with pulmonary edema is seen in?
A. Left atrial Myxoma *(NBE)*
B. High altitude
C. Mitral stenosis
D. LV systolic dysfunction

156. ARDS is associated with *(PGI Dec-04)*
A. Acute pancreatitis
B. Trauma
C. Severe Falciparum malaria
D. All of the above

157. A patient comes with sudden respiratory distress, on examination, bilateral basal crepts are present over chest suggestive of pulmonary edema with normal alveolar wedge pressure. The likely cause is
A. Narcotic overdose *(AIIMS June 2000)*
B. Congestive heart failure
C. Myocardial infarction
D. Cardiogenic shock

158. Which of the following is the most characteristic feature of Adult Respiratory Distress Syndrome (ARDS): *(AI 2012)*
A. Diffuse Alveolar Damage
B. Hypoxemia and Hypoxia
C. Surfactant Deficiency
D. Hypocapnia

159. All are seen in ARDS, *except* : *(AIIMS May 95)*
A. Pulmonary edema
B. Decreased tidal volume.
C. Hypercapnia
D. Decreased compliance

160. Which of the following is not seen in ARDS: *(NBE)*
A. Pulmonary edema
B. Hypoxemia
C. Stiff lung
D. Hypercapnia

161. All of the following features can seen in ARDS except: *(NBE)*
A. Pulmonary Shunting
B. Reduced compliance
C. Hypoxemia
D. Hypercapnia

162. Which of the following is not seen in ARDS:
A. Pulmonary edema *(AI 1996)*
B. Hypoxemia

C. Stiff lung
D. Hypercapnia

163. Which of the following is not seen in ARDS (NBE)
A. Hypoxemia
B. Hypercapnia
C. Pulmonary edema
D. Stiff lung

164. In ARDS, not true is – (PGI June 99)
A. Decreased pulmonary compliance
B. Increased pulmonary artery pressure
C. Increased left atrial pressure
D. Severe hypoxemia

165. Feature of shock lung is- (AIIMS Nov 07)
A. Diffuse alveolar damage
B. Usual interstitial penumonitis
C. Organizing pneumonia
D. Bronchilolitis

166. Acute Lung Injury (ALI) is characterized by all except (NBE)
A. $PaO_2/FiO_2 < 200mm\ Hg$
B. Bilateral interstitial infiltrates
C. PCWP <18 mm Hg
D. Normal Left atrial pressure

167. Acute Lung injury is characterized by all, Except:
A. Alveolar infiltrates (PGI Dec
B. Hypoxemia
C. Pulmonary shunting
D. $PaO_2/FlO_2$ <200mm of Hg
E. None of the above

## Pulmonary Thromboembolism

168. A patient with fracture pelvis is admitted in ICU after surgery. Post operatively he develops sudden dyspnea and chest pain. The likely cause is :
A. Pulmonary thromboembolism (AIIMS Nov 99)
B. Shock
C. Respiratory infection
D. ARDS

169. All are true about pulmonary embolism, except :
A. Chest pain is the most common symptom
B. Most commonly presents within 2 weeks
C. More is the survival time, more is the chance of recovery (AIIMS May 94)
D. Arises from leg veins

170. A 60 year old woman with fracture neck of femur presents to the emergency department a few days after her injury with sudden onset breathlessness and chest pain. The most likely diagnosis is: (NBE)
A. Myocardial Infarction
B. Deep Vein Thrombosis
C. Pulmonary Embolism
D. Pleuritis

171. The most common cause of preventable Hospital Death is (NBE)
A. Acute Pulmonary Embolism
B. Heart Failure
C. Myocardial Infarction
D. Cancer

172. The most common cause of Pulmonary thromboembolism (NBE)
A. DIC
B. Coagulation Disorder
C. DVT
D. Venous Hypertension

173. The most common source of pulmonary embolism is:
A. Amniotic fluid embolism (AIIMS May 95)
B. Calf vein thrombi
C. Large veins of leg
D. Cardio thoracic surgery

174. All of the following conditions may predispose to pulmonary embolism except: (AI 2003)
A. Protein S deficiency
B. Malignancy
C. Obesity
D. Progesterone therapy

175. In acute pulmonary embolism, the most frequent ECG finding is :
A. S1Q3T3 pattern (AIIMS May' 06)
B. P. pulmonale
C. Sinus tachycardia
D. Right axis deviation

176. D-Dimer values may be increased in all of the following Except: (NBE)
A. Myocardial infarction
B. Pneumonia
C. Anticoagulant therapy
D. Pregnancy

177. D-dimer is the most sensitive diagnostic test for –
A. Pulmonary embolism AIIMS May 05)
B. Acute pulmonary oedema
C. Cardiac tamponade
D. Acute myocardial infarction

178. D-Dimer is the most sensitive test for (NBE)
A. DVT
B. Pulmonary Embolism
C. Acute Pulmonary adema
D. Acute myocardial infarction

179. Best investigation when there is clinical suspicion of pulmonary embolism in a patient is- (NBE)
A. D-Dimmer Assay
B. Multidetector CT angiography
C. Doppler ultrasound
D. Catheter angiography

180. A 55 year old man who has been on bed rest for the past 10 days, complains of breathlessness and chest pain. The chest X-ray is normal. The next investigation should be: (AI 2003) (AI 2004)
A. Lung ventilation-perfusion scan
B. Pulmonary arteriography
C. Pulmonary venous angiography
D. Echocardiography

181. The most definitive method of diagnosing pulmonary embolism is : *(AIIMS Nov. 05)*
A. Pulmonary aterigraphy
B. Radioisotope perfusion pulmonary scintigraphy
C. EKG
D. Venography

182. The treatment of choice in a patient with Massive Pulmonary Embolism in Shock is: *(NBE)*
A. Thrombolytic Therapy
B. Low Molecular Weight Heparin
C. Aggressive fluid resuscitation
D. Diuretic Therapy

183. A young patient presents to the Emergency with Acute pulmonary embolism. Patient's blood pressure is normal but echocardiography reveals Right ventricular hypokinesia and compromised cardiac output.
The treatment of choice in this patient is:
A. Thrombolytic therapy *(AIIMS Nov 2001)*
B. Anticoagulation with low molecular weight heparin
C. Anticoagulation with warfarin
D. Inferior vena cora filters

## Pulmonary Hypertension

184. Pulmonary Hypertension is defined as Pulmonary Artery Pressure: *(NBE)*
A. ≥15mm Hg
B. ≥18mmHg
C. ≥20mmHg
D. ≥25mmHg

185. Pre-capillary Pulmonary Hypertension is defined as: *(NBE)*
A. PAP ≥25 mm Hg; PCWP >15mmHg
B. PAP ≥25mmHg; PCWP ≤15mm Hg
C. PCWP ≥25mmHg; PAP >15mmHg
D. PCWP ≥25mmHg; PAP ≤15mmHg

186. All of the following are signs of Pulmonary Hypertension, except: *(NBE)*
A. Right Parasternal Heave
B. Raised JVP
C. Palpable P2
D. Low Volume Pulse

187. In primary pulmonary hypertension basic abnormality in gene lies in: *(AIIMS May 07)*
A. Bone morphogenic protein receptor II
B. Endothelin
C. Homebox gene
D. PAX – 11

188. Not seen in pre capillary pulmonary hypertension:
A. ↑ pressure in pulm. circulation *(PGI June 98)*
B. ↑ capillary pressure
C. Rt-vent.hypertrophy
D. ↑ Pulmonary wedge pressure

189. Precapillary Pulmonary hypertension is caused by all Except: *(PGI June 03)*
A. Mitral stenosis
B. Pulmonary vasculitis
C. Primary pulmonary hypertension
D. Thromboembolism

190. All are causes of pulmonary hypertension except-
A. Hyperventilation *(AIIMS Nov 07)*
B. Morbid obesity
C. High altitude
D. Fenfluramine

191. Pulmonary hypertension may occur in all of the following conditions except- *(AIIMS Nov 06)*
A. Toxic oil syndrome
B. Progressive systemic sclerosis
C. Sickle cell anemia
D. Argemone mexicana poisoning

192. Pulmonary hypertension in COPD is due to all, Except: *(PGI Dec 97)*
A. Hypoxia
B. Pulmonary vasoconstriction
C. High lung volume
D. Bronchoconstriction

193. Iloprost in Pulmonary Arterial Hypertension is administered: *(NBE)*
A. Intravenous
B. Intramuscular
C. Oral
D. Inhalation

194. A 29 year old unmarried female presents with progressive dyspnea. Her X ray chest shows clear lung fields. Pulmonary function testing reveals in FVC of 92%; FEV1/FVC of 89%; and dlCO of 59%. On exercise testing her oxygen saturation drops from 92% to 86%. What is the likely diagnosis:
A. Alveolar hypoventilation *(AIIMS Nov 2008)*
B. Primary pulmonary hypertension
C. Interstitial lung disease
D. Anxiety

195. A 29 year old anxious lady presents with a history of progressive breathlessness and exercise intolerance since four months. Her FVC is 90% and FEV1 / FVC is 86%. Oxygen saturation after exercise was observed to drop from 92% to 86%. What is the likely diagnosis : *(AI 2010)*
A. Primary alveolar hypoventilation
B. Primary pulmonary hypertension
C. Anxiety disorder
D. Interstitial lung disease

196. Chronic Cor pulmonale is seen in all except:
A. Pulmonary embolization *(PGI-Dec-04)*
B. COPD
C. Cystic fibrosis
D. Primary pulmonary hypertension

197. The most common cause for chronic cor pulmonale is
A. Recurrent pulmonary embolization *(PGI Dec 04)*
B. COPD
C. Cystic fibrosis
D. Bronchial Asthma
E. Airway foreign body

198. The most common cause of acute cor pulmonale is:
A. Pneumonia. *(AIIMS Nov 02)*
B. Pulmonary thromboembolism.
C. Chronic obstructive pulmonary disease.
D. Primary spontaneous pneumothorax.

199. All the following are radiological features of Chronic Cor pulmonale except- *(NBE)*
A. Kerley B lines
B. Prominent lower lobe vessels
C. Pleural effusion
D. Cardiomegaly

## Pleural Diseases

### Pleural Effusion

200. Which one of the following conditions may lead to exudative pleural effusion *(AI 2003)*
A. Cirrhosis
B. Nephrotic syndrome
C. Congestive heart failure
D. Bronchogenic carcinoma

201. All of the following are Light's criteria for exudative pleural effusion: *(NBE)*
A. Pleural fluid protein to serum protein > 0.5
B. Pleural fluid LDH to serum LDH > 0.6
C. Pleural fluid LDH is > 2/3 times the normal upper limit for serum
D. Pleural fluid ADA to Serum ADA <16

202. Which of the following is NOT a feature of an exudate? *(NBE)*
A. Proteins< 3gm
B. Cells> 1000/mi
C. Cloudy appearance
D. Cells predominantly are neutrophils

203. All of the folowing are features of Exudative effusions, Except: *(NBE)*
A. Serum : Pleural Albumin ratio < 1.2mg/dl
B. Pleural flud cholesterol > 55
C. Fluid:Serum Protein ratio > 0.5
D. Fluid : Serum Protein ratio >0.5

204. All of the following are causes of Transdative pleural effusion Except: *(PGI-June-02)*
A. Nephrotic syndrome
B. Rheumatoid arthritis
C. Constrictive pericarditis
D. Myxedema
E. Pulmonary embolism

205. Left –sided pleural effusion seen in *(PGI- June- 02)*
A. Pancreatitis
B. Rheumatoid arthritis
C. Hypoproteinemia
D. CCF
E. Esophageal rupture

206. All of the following are true about pleural effusion, Except: (select two options) *(NBE)*
A. Horizontal fluid level
B. Decreased lung volume
C. Decreased heart sounds
D. Decreased chest movement
E. Succussion splash

207. Tuberculous pleural effusion is characterised by all of the following features *except* effusion :
A. Harmorrhagic effusion *(AI 1997)*
B. Pleural fluid LDH more than 60% that of serum LDH.
C. Increased deaminase
D. Increased mesothelial cells

208. Pleural fluid having low glucose is seen in all, except-
A. Tuberculosis *(AIIMS May 93)*
B. Empyema
C. Mesothelioma
D. Rheumatoid arthritis

209. All of the following show low glucose in pleural fluid, EXCEPT- *(AIIMS Dec 94)*
A. Empyema
B. Malignant pleural effusion
C. Rheumatoid arthritis
D. Dressler's syndrome

210. Low glucose in pleural effusion is seen in all, *except*
A. Dressler syndrome *(AIIMS May 94)*
B. Empyema
C. Malignant pleural effusion
D. Rheumatoid arthritis

211. Decreased Glucose in pleural effusion is seen in: (Select best two correct options) *(PGI June 99)*
A. Rheumatoid arthritis
B. SLE
C. Pneumococcal infection
D. P.carinii infection

212. A high amylase level in pleural fluid suggests a diagnosis of *(AIIMS May 03)*
A. Tuberculosis
B. Malignancy
C. Rheumatoid arthritis
D. Pulmonary infarction

213. Amylase increased in pleural fluid is seen in following except: *(PGI June 2000)*
A. Rheumatoid arthritis
B. Esophageal perforation
C. Malignancy
D. Gall stone pancreatitis

214. Presence of cholesterol crystal in pleural effusion is a feature of: *(AIIMS June 97)*
A. Myxoedema
B. Hypertriglyceridemia
C. Hyperthyroidism
D. Sarcoidosis

215. In an adult patient with plural effusion, the most appropriate site for plurisentesis done by inserting a needle is in: *(AI 2002)*
A. 5th intercostals space in midclevicular line
B. 7th intercostal space in mid axillary's bone
C. 2nd intercostals space adjacent to the sternum
D. 10th intercostal space adjacent to the vertebral column

## Pneumothorax

216. Pneumothorax is seen in all, except-
A. Marfan syndrome *(AIIMS May 94)*
B. Assisted ventilation
C. Eosinophilic granuloma
D. Bronchopulmonary Aspergillosis

217. While inserting a central venous catheter, a patient develops respiratory distress. The most likely cause is: *(AI 2002)*
A. Hemothorax
B. Pneumothorax
C. Pleural effusion
D. Hypovolumia

218. All of the following are characteristic features of primary spontaneous penumotharax Except
A. Male gender *(AIIMS 92)*
B. Old age
C. Tall stature
D. History of smoking

219. Spontaneous pneumothorax is commonly seen in:
A. Smokers *(PGI June 02)*
B. Young females
C. Old age
D. Short statured men

220. Which of the following is true about Pneumothorax?
A. Decreased Chest Expansion *(NBE)*
B. Increased Breath Sounds
C. Increased Vocal Resonance
D. Dull percussion note

221. Which of the following statements about pneumothorax is true: *(AIIMS Dec 94)*
A. Breath sounds are increased
B. Percussion note is decreased
C. Always needs chest tube insertion
D. Often needs chest tube insertion

222. A 34 year old male with chest trauma presents with sudden onset respiratory distress which is increasing. Hyper-resonant note is observed on the left side. Which of the following is the most appropriate immediate emergent management? *(NBE)*
A. Needle puncture and emergent decompression
B. Tube insertion
C. Antibiotic and oxygen
D. No treatment needed.

223. A 30 year old female comes acute breathlessness, neck vein distention, and absent breath sounds and nediastinal shift. Which of the following should be done immediately? *(PGI June 2008)*
A. HRCT is the investigation of choice
B. ABG analysis should be done
C. CXR
D. Large bore needle puncture of pleura

224. A patient with history of chest trauma presents to the emergency department in severe respiratory distress with a BP of 90/70 mm Hg and a Pulse rate of 120/min. The most likely diagnosis is: *(NBE)*
A. Simple Pneumothorax
B. Hemothorax
C. Cardiac tamponade
D. Tension Pneumothorax

225. A patient with history of chest trauma presents to the emergency department with a BP of 90/70 mm Hg and a Pulse rate of 120/min. The patient is observed to be short of breath using his accessary muscle of respiration. The JVP is not elevated. The most likely diagnosis is: *(NBE)*
A. Tension Pneumothorax
B. Massive Hemothorax
C. Cardiac tamponade
D. None of the above

226. In left sided massive pneumothorax, ECG shows all, *except :* *(AIIMS May 94)*
A. Left axis deviation
B. Absent R wave
C. Peaked P wave
D. Precordial T wave inversion

227. IPPV can cause all of the following *except*:
A. Barotrauma *(AI 2001)*
B. Pleural effusion
C. Missing
D. None of the above

## Disorders of Ventilation and Mediastinitis

228. "Sleep apnoea", is defined as a temporary pause in breathing during sleep lasting at least-
A. 40 seconds *(AIIMS May 03)*
B. 30 seconds
C. 20 seconds
D. 10 seconds

229. Duration of apnea in obstructive sleep apnea syndrome is: *(NBE)*
A. >10 sec
B. >20 sec
C. >30 sec
D. >60 sec

230. The Epworth scale is used for assessing:
A. Body mass index *(NBE)*
B. Vital capacity in post-operative patients
C. Sleep apnea
D. Risk of embolism in perioperative patient

231. True about primary pulmonary hypoventilation is:
A. Does not respond to chemical stimuli
B. Hypocapnoea and normal $PaO_2$
C. Common in children *(AIIMS Feb 97)*
D. Respiratory alkalosis is diagnostic

232. All are true about bilateral diaphragmatic paralysis, *except* : *(AIIMS May 95)*
A. Sniff test is positive
B. Causes normocapnic failure
C. Diaphragmatic pacing is useful if any nerve is intact
D. None of the above

233. Most common cause of Mediastinitis is:
A. Tracheal rupture *(AIIMS 97)*
B. Esophageal rupture
C. Drugs
D. Idiopathic

## Lung (Bronchogenic) Tumors

### Bronchogenic carcinoma

234. Most common bronchogenic carcinoma is
A. Small cell carcinoma *(AIIMS June 2000)*
B. Squamous cell carcinoma
C. Mixed cell carcinoma
D. Adenocarcinoma

235. Most common type of carcinoma lung is-
A. Small cell carcinoma *(AIIMS May 93)*
B. Adenocarcinoma
C. Squamous cell carcinoma
D. Large cell carcinoma

236. All of the following are true regarding oat cell carcinoma of lung, *except*: *(AIIMS June 99)*
A. Varient of large cell anaplastic CA
B. Chemotherapy is effective
C. Paraneoplastic syndrome may be present
D. Causes SIADH

237. All of the following statements about small cell carcinomas are true, Except *(PGI-June- 06)*
A. Commonest Malignancy of lung
B. Associated with parancoplastic syndrome
C. Cause SVC obstruction
D. Chemosensitive
E. Commonly metaslistre to brain

238. Which of the following statements about small cell carcinoma is true? *(AI 2009)*
A. Bone metastasis is uncommon
B. Peripheral in location
C. Chemosensitive tumor
D. Paraneoplastic syndrome with ↑PTH is common

239. All of the following statements about Non Small Cell Carcinoma of Lung (NSCCL) are true, Except:
A. Contralateral mediastinal nodes are a contraindication to surgical resection *(AI 2012)*
B. Single Agent Chemotherapy is preferred for patient > 70 years with advanced disease
C. Squammous Cell Carcinoma is the most common NSCCL amongst Asian population
D. Gefitinib is most effective for female smokers with adenocarcinoma on histology

240. In a chronic smoker, a highly malignant aggressive and metastatic lung carcinoma is :
A. Squamous cell Carcinoma *(AIIMS May 01)*
B. Small cell Carcinoma
C. Adenocarcinoma
D. Large cell carcinoma

241. Following hormonal levels are increased in small cell carcinoma of lung *except* : *(AI 1997)*
A. ACTH
B. Growth hormone
C. ANF
D. AVP

242. Type of lung carcinoma producing superior vena cava syndrome: *(AIIMS June 97)*
A. Squamous cell carcinoma
B. Adenocarcinoma
C. Small cell carcinoma
D. Anaplastic carcinoma

243. Carcinoma lung responding best to chemotherapy-
A. Squamous cell type *(NBE)*
B. Oat cell type
C. Adenocarcinoma
D. All respond equally

244. Clubbing is least common in: *(AIIMS Dec 97)*
A. Squamous cell carcinoma
B. Adenocarcinoma
C. Small cell carcinoma of lung
D. Mesothelioma

245. A 60 year old man presents with non productive cough and haemoptysis for 4 weeks; He has grade III clubbing, and a lesion in the apical lobe on x ray. Most likely diagnosis here is :
A. Small cell ca *(AI 2001) (AIIMS June 2000)*
B. Non small cell ca
C. Fungal infection
D. Tuberculosis

246. What is TRUE regarding adenocarcinoma lung
A. Causes 50% of lung cancers *(AIIMS Dec 94)*
B. Unlikely histological variant in young patients
C. Associated with subcutaneous angiomyolipoma
D. Peripheral location

247. True statement about adenocarcinoma lung are (Choose two best options): *(PGI June 05)*
A. Common in females
B. Not associated with smoking
C. Central cavitation is a charachteristic feature
D. Peripheral involvement is common
E. Upper lobe involvement is common

248. Commonest type of lung carcinoma in nonsmokers is
A. Squamous cell carcinoma *(AIIMS Dec 94)*
B. Adenocarcinoma
C. Alveolar cell carcinoma
D. Small cell carcinoma

249. Lung to lung metastasis is seen in- *(NBE)*
A. Adenocarcinoma of lung
B. Squamous cell carcinoma
C. Small cell carcinoma
D. Neuroendocrine tumor of lung

250. A patient presents with secondaries to the adrenals. The most common site of primary is :
A. Lung *(AI 2000)*
B. Kidney
C. Breast
D. Stomach

251. Which of the following statements about lung carcinoma is true *(AI 2010)*
A. Squammous cell variant accounts for 70% of all lung cancers
B. Oat cell variant typically present with cavitation
C. Oat cell variant is typically associated with hilar adenopathy
D. Adenocarcinoma variant is typically central in location

252. Most common symptom of lung carcinoma
A. Cough *(AIIMS 90)*
B. Dyspnoea
C. Weight loss
D. Chest pain

253. The commonest intrabronchial cause of haemopysis is
A. Carcinoma lung *(AIIMS May 95)*
B. Adenoma lung
C. Emphysema
D. Bronchiectasis

254. A 60 years old chronic smoker presents with complaints of hemoptysis. Her chest X-ray appears to be normal. What is the next best investigation:
A. Bronchoscopy *(AIIMS Nov. 2000)*
B. High resolution CT
C. Sputum cytology
D. Pulmonary function test

255. A 60 year old man is suspected of having bronchogenic ca: TB has been ruled out in this pt. What should be the next investigation- *(AI 01)*
A. CT guided FNAC
B. Bronchoscopy and biopsy
C. Sputum cytology
D. X-Ray chest

256. A 60 yr old man is suspected of having bronchogenic ca; TB has been ruled out in this pt.What should be the next investigation :
A. CT guided FNAC *(AI 2001)*
B. Bronchoscopy and biopsy
C. Sputum cytology
D. X-Ray chest.

257. A patient presents with a cavitatory lesion in right upper lobe of lung. The best investigation is –
A. Branchoscopy, lavage and brushing *(AI 2000)*
B. C.T. Scan
C. X ray
D. FNAC

258. A patient presents with a cavitatory lesion in right upper lobe of lung. The best investigation is-
A. Branchoscopy, lavage and brushing *(AI 2000)*
B. C.T. Scan
C. X ray
D. FNAC

259. Serum ACE may be raised in all of the following *except* : *(AI 2005)*
A. Sarcoidosis
B. Silicosis
C. Berylliosis
D. Bronchogenic carcinoma

260. A 60 year old male was diagnosed as carcinoma right lung. On CECT chest there was a tumor of 5x5 cm in upper lobe and another 2x2 cm size tumor nodule in middle lobe. The primary modality of treatment is :
A. Radiotherapy *(AI 2004)*
B. Chemotherapy
C. Surgery
D. Supportive treatment

261. Ramesh 40 yrs male patient presenting with polyuria, pain abdomen, nausea, vomiting, altered sensorium was found to have bronchogenic carcinoma. The electrolyte abnormality seen in him would be:
A. Hypokalemia *(AIIMS May 02)*
B. Hyperkalemia
C. Hypocalcaemia
D. Hypercalcemia

262. A 60 year old male presented to the emergency with breathlessness, facial swelling and dilated veins on the chest wall. The most common cause is: *(AI 2003)*
A. Thymoma
B. Lung cancer
C. Hodgkin's lymphoma
D. Superior vena caval obstruction

263. Which of the following tumor is most commonly associated with superior vena cava syndrome:
A. Lymphoma *(AI 2011)*
B. Small cell carcinoma
C. Non small cell carcinoma
D. Metastasis

## Cystic Fibrosis

264. Which of the following systems is least likely to be affected in cystic fibrosis *(NBE)*
A. Respiratory
B. Genitourinary

C. Hepatobiliary
D. Endocrine

265. The most common cause of pulmonary infection in cystic fibrosis is *(NBE)*
A. Pseudomonas Aeroginosa
B. Staphylococcus Aureus
C. Bukholderia cenocapacea
D. Nontuberculous mycobacteria

266. Most common pathogen causing, pulmonary infection in cystic fibrosis in infants & young children is *(NBE)*
A. Staphylococcus Aureus
B. Pseudomonas Aeroginosa
C. Bukholderia Cenocapacea
D. Nontubercular mycobacteria

267. An infant has a positive newborn screening test for cystic fibrosis. What cut off of sweat chloride strongly suggests cystic fibrosis: *(NBE)*
A. Sweat Chloride >30
B. Sweat Chloride >40
C. Sweat Chloride >50
D. (d) Sweat Chloride >60

268. Finger in glove sign results from:
A. ABPA *(NBE)*
B. Cystic Fibrosis
C. Tuberculosis
D. Bronchocoele

## Bronchial Ademoma and Bronchial Cysts

269. Bronchial adenoma commonly present as : *(NBE)*
A. Recurrent hemoptysis
B. Cough
C. Dysponea
D. Chest pain

270. Which of the following statements about Branchial cysts is true: *(AI 1993)*
A. 50-70% are seen in lungs
B. Most common site is mediastinum
C. They are premalignant lesions
D. Infection is uncommon in Pulmonary bronchogenic cysts

## Kartagener's Syndrome

271. All of the following are true about Kartagener's syndrome, Except *(PGI-Dec-04)*
A. Dextrocardia
B. Infertility
C. Mental retardation
D. Bronchiectasis

272. Kartagener's syndrome includes all of the following, Except : *(PGI June 01)*
A. Situs inversus
B. Bronchiectasis
C. Sinusitis
D. Male infertility
E. Cystic fibrosis

## Pulmonary Renal Syndrome

273. Causes of pulmonary renal syndrome: *(PGI June 07)*
A. Leptospirosis
B. Hanta virus
C. Paraquat poisoning
D. All of the above

274. A patient presents with hemoptysis and hematuria few weeks after a respiratory tract infection. ANCA antibodies are present. Likely diagnosis is:
A. Goodpasture's syndrome *(AI 1995)*
B. IgA Nephropathy
C. Nephrotic syndrome
D. PSGN

275. Rama, a 20 year old smoker, presents with hemoptysis and hematuria. Likely diagnosis is:
A. Good pasture's syndrome *(AI 1997)*
B. Nephrotic syndrome
C. Gullian Barre syndrome
D. IgA Nephropathy

## Neonate Alveolar Proteinosis

276. A male born at term after an uncomplicated pregnancy, labor and delivery develops severe respiratory distress within a few hours of birth. Results of routine culture were negative. The chest roengogram reveals a normal heart shadow and fine reticulonodular infiltrates radiating from the hilum. ECHO findings reveal no abnormality. Family history reveals similar clinical course and death of a male and female sibling at 1 month and 2 months of age respectively. The most likely diagnosis is: *(AI 2008)*
A. Neonatal Alveolar Proteinosis
B. Total Anomalous Pulmonary Venous Circulation (TAPVC)
C. Meconium Aspiration Syndrome
D. Diffuse Herpes simplex infection

277. 3.5 kg term male baby, born of uncomplicated pregnancy, developed respiratory distress at birth, not responded to surfactant, ECHO finding revealed nothing abnormal, X-ray showed ground glass appearance and culture negative. Apgars 4 and 5 at 1 and 5 minutes. History of one month female sibling died before. What is the diagnosis? *(AIIMS Nov 07)*
A. TAPVC
B. Meconium aspiration
C. Neonatal pulmonary alveolar proteinosis
D. Diffuse herpes simplex infection

## Symptoms and Signs of Respiratory Disease

278. Which of the following is least likely cause of hemoptysis *(PGI June 07)*
A. Pneumonia
B. Empyema
C. Bronchiectasis
D. Metral stenosis

279. Cavernous Respiration is seen in: *(NBE)*
   A. Cavity
   B. Consolidation
   C. Fibrosis
   D. Interstitial Inflammation

280. Which of the following is not a feature of consolidation *(NBE)*
   A. Increased vocal resonance
   B. Dull Percussion note
   C. Bronchial Breath sounds
   D. Tracheal shift to side of consolidation

281. A patient presents with sudden onset of breathlessness after a subclavian vein cannulation. On examination, breath sounds are absent while the chest is hyper-resonant on percussion on one side. Most likely cause is: *(AI 2012)*
   A. Iatrogenic Pneumothorax
   B. Subclavian Vein air embolus
   C. Malposition of cannula
   D. Cardiac Arrhythmia

282. The most common site of bleeding in Hemoptysis is
   A. Tracheobronchial tree *(NBE)*
   B. Pulmonary Parenchyma
   C. Pleural Disease
   D. All of the above

283. The artery most frequently responsible for bleeding in massive hemoptysis is *(NBE)*
   A. Bronchial Artery
   B. Pulmonary Artery
   C. Intersegmental Artery
   D. Intercostal Artery

284. Pulmonary Apoplexy is seen in: *(NBE)*
   A. Mitral Stenosis
   B. Mitral Regurgitation
   C. AorticStenosis
   D. Aortic regurgitation

285. All of the following statements about central cyanosis are true Except: *(NBE)*
   A. Central cyanosis becomes evident when reduced haemoglobin < 5g/dl
   B. Chronic Asthma may cause central cyanosis
   C. Alveolar Hypoventilation causes central cyanosis
   D. Methemoglobinemia causes central cyanosis

286. Cause of central cyanosis include all of the following, Except *(NBE)*
   A. Chronic Asthma
   B. Congenital Pulmonary stenosis
   C. Congestive heart failure
   D. Alveolar hypoventilation

287. Cyanosis NOT improving with 100% oxygen in case of: *(AIIMS May 93)*
   A. Cardiac Asthma
   B. Interstitial lung disease
   C. Bronchial asthma
   D. Tetralogy of Fallot (TOF)

288. One of the following condition is not associated with clubbing : *(AIIMS Dec 98)*
   A. Primary biliary cirrhosis
   B. Chronic bronchitis
   C. Cryptogenic fibrosing alveolitis
   D. Central bronchiectasis

289. Causes of unilateral clubbing include all of the following, Except *(PGI June 05)*
   A. Congenital cyanotic heart disease
   B. Panicoast tumor
   C. Aortic Ancurym
   D. Brachial AV fistulas

290. Hypoxemia seen in: *(PGI June 02)*
   A. Hypoventilation
   B. Decreased $Fio_2$
   C. Myasthenia gravis
   D. Pulmonary emboli
   E. All of the above

291. Platypnea may be seen in all of the following conditions, except *(PGI June 05)*
   A. Bilateral Diaphragmatic palsy
   B. Pleural effusion
   C. Pulmonary embolism
   D. Cirrhosis
   E. COPD

292. Homogenous opacification of right hemithorax with right sided shift of mediastinum may be caused by
   A. Collapse of Right lung *(PGI June 97)*
   B. Consolidation of Right lung
   C. Right sided hemothorax
   D. Left sided hydrothorax
   E. All of the above

293. A child develops acute respiratory distress, stridor, hyperinflation on one side of chest with decreased breath sound on that side. Most likely cause is :
   A. Asthma *(AIIMS June 2000)*
   B. Aspiration pneumonia
   C. Foreign body aspiration
   D. Pleural effusion

## Miscellaneous

294. Bilateral Rhonchii may be seen in all of the following Except *(PGI June 08)*
   A. Pulmonary Edema
   B. Bronchiectasis
   C. Pulmonary Embolism
   D. Emphysema

295. Static compliance is decreased in all of the following except: *(PGI 2000)*
   A. ARDS
   B. Pulmonary edema
   C. Interstial fibrosis
   D. Fibrosing alveolitis
   E. Emphysema

296. Pulmonary Compliance is decreased in all of the following conditions, Except: *(AI 2011)*
   A. Pulmonary Congestion
   B. COPD
   C. Decreased Surfactant
   D. Pulmonary Fibrosis
297. Thickening of pulmonary alveolar – capillary membrane is seen in : *(PGI June 07)*
   A. Asthma
   B. Bronchitis
   C. Pulmonary fibrosis
   D. Emphysema
298. Smoking is generally not associated as a risk factor with- *(AI 06)*
   A. Small cell carcinoma
   B. Respiratory bronchiolitis
   C. Emphysema
   D. Bronchiolitis obliterans organizing pneumonia
299. All are cavitating lesions in the lungs, except-
   A. Caplan's syndrome *(AIIMS May 94)*
   B. Hamartoma
   C. Wegner's granuloma
   D. Squamous cell carcinoma
300. Which of the following statements is true about High Attitude Pulmonary Edema (HAPE)?
   A. Not exacerbated by exercise *(AIIMS Nov. 06)*
   B. Associated with pulmonary vasoconstriction
   C. Occurs only in unacclamatized individuals
   D. Associated with low cardiac output
301. Bronchial hyperplasia may be caused by all except-
   A. Smoking *(NBE)*
   B. Theophylline
   C. Prematurity
   D. Allergy
302. Most common cause of amoebic lung abscess is :
   A. Aspiration *(AI 1997)*
   B. Direct spread from liver
   C. Hematogenous spread from liver
   D. Hematogenous spread from gut
303. Floating water lilly sign on chest x-ray is characteristic of: *(NBE)*
   A. Hydatid cyst
   B. Lung abscess.
   C. Empyema thoracis
   D. Ruptured amebic liver abscess.
304. Measurements of intravacular pressure by a pulmonary artery catheter should be done: *(AI 2002)*
   A. At end expiration
   B. At peak of inspiration
   C. During mid inspiration
   D. During mid expiration
305. A 62 years old man with carcinoma of lung presented to emergency department with respiratory distress. His EKG showed electrical alternans. The most likely diagnosis is : *(AIIMS May 03)*
   A. Pneumothorax.
   B. Pleural effusion.
   C. Cardiac tamponade.
   D. Constrictive pericarditis.
306. The most common fetal response to acute hypoxia is:
   A. Tachycardia *(AI 2009)*
   B. Tachypnea
   C. Bradycardia
   D. Ventricular Arrhythmia
307. Hypersensitivity Pneumonitis is classically described as a: *(AI 2009)*
   A. Type I hypersensitivity reaction
   B. Tye II hypersensitivity reaction
   C. Type III (Immune complex) Hypersensitivity
   D. Type IV (Cell mediated) Hypersensitivity
308. A child presented with severe respiratory distress two days after birth.On examination he was observed to have a scaphoid abdomen and decreased breath sounds on the left side. He was managed by prompt Endotracheal intubation .After ET tube placement the maximal cardiac impulse shifted further to the right side. What should be the next step in management?
   A. Confirm the position of endotracheal tube by chest X ray *(AI 2008)*
   B. Remove tube and reattempt intubation
   C. Nasogastric tube insertion & decompress the bowel
   D. Chest X ray to confirm diagnosis
309. A child presented with severe respiratory distress two days after birth. On examination he was observed to have a scaphoid abdomen and decreased breath sounds on the left side. He was managed by prompt Endotracheal intubation. After ET tube placement the maximal cardiac impulse shifted further to the right side. What should be the next step in management?
   A. Confirm the position of endotracheal tube by chest X ray *(AI 2008)*
   B. Emergency surgery
   C. Nasogastric tube insertion & decompress the bowel
   D. Chest X ray to confirm diagnosis
310. A $7_{1/2}$ months old child with cough, mild stridor is started on oral antibiotics. The child showed initial improvement but later developed wheeze, productive cough, and mild fever. X–ray shows hyperlucency and PFT shows an obstructive curve. The most probable diagnosis is, *(AI 2008)*
   A. Bronchiolitis obliterans
   B. Post viral syndrome
   C. Pulmonary alveolar microlithiasis
   D. Follicular bronchitis
311. Respiratory centre depression is caused by all of the following, Except: *(AIIMS Nov 2010)*
   A. Opium
   B. Strychnine
   C. Barbiturates
   D. Gelsemium

312. Which of the following is the correct full form of 'APACHE'? *(NBE)*
   A. Acute pulmonary and cardiac health evaluation
   B. Acute physiology and chronic health evaluation
   C. Adult pediatric and cardiac health evaluation
   D. Adolescent pediatric and child health evaluation

313. Mendelson's syndrome refers to:
   A. Aspiration of gastric content *(NBE Pattern14-15)*
   B. Rupture of bronchial tuberculoma.
   C. Transient pneumonitis of allergic origin
   D. Tracheal compression due to nodal eniargement

314. Antibody used in treatment of RSV infection is:
   A. Omalizumab *(NBE)*
   B. Palivizumab
   C. Rituximab
   D. Daclizumab

315. Which of the following drugs, is used for Smoking Cessation? *(NBE)*
   A. Naltrexone
   B. Bupropion
   C. Buprenorphine
   D. Methadone

## ANSWERS, REFERENCES, EXPLANATIONS AND RELEVANT HIGH YIELD FACTS

### Respiratory failure & Disturbance in Respiratory Functions

**1. Answer is D (Normal A-a gradient):** *Harrison 16th/1583,1584; 17th/1590; API 8th/1286; Refer previous question*

***Type I Respiratory failure is characterized by an increase in alveolar arterial $O_2$ gradient.***

***Respiratory failure*** *is defined as a disorder wherein, lung function is inadequate to meet the metabolic demands of the individual and is unable to maintain normal arterial gas levels in the blood.*

**It is of two types:**

| Type I Respiratory failure | Type II Respiratory failure |
|---|---|
| Represents failure of oxygenation and is characterized by a low $PaO_2$ with normal or low $PaCO_2$.<br>$PaO_2$ : Low (< 60 mm Hg)<br>$PaCO_2$ : Normal or low (≤ 49 mm Hg)<br>$P_{A-a}O_2$ : Increased | Represents a defect in ventilation (hypoventilation) and is characterized by decreased $PaO_2$ with increase $PaCO_2$.<br>$PaO_2$ : Decreased (< 60 mm Hg)<br>$PaCO_2$ : Increased (> 49 mm Hg)<br>$P_{A-a}O_2$ : Normal |
| **Causes :** | **Causes :** |
| This type is caused by conditions which affect oxygenation, like:<br>• Parenchymal diseases (V-Q mismatch)<br>• Diseases of vasculature/shunts<br>Examples:<br>- Pneumonia Q<br>- ARDS Q<br>- Emphysema Q<br>- Right to left shunts Q | This type is caused by conditions causing hypoventilation as in:<br>• Obstructive lung disease: COPD, F. body<br>• Decreased central respiratory drive e.g. CNS disorders like : Brain injury, Meningitis<br>• Weakness of respiratory muscle e.g.<br>- Peripheral N.S. disorders like: M. gravis.<br>- Interstitial lung disease. Q<br>- MS disorders like polymyositis.<br>- Rib cage disorders : Kyphoscoliosis. |

**2. Answer is B (Low $PO_2$ and high $PCO_2$):** *Harrison 18th/p 2200 Harrison 17th/1676; API Medicine 6th/ 278; 8th/1287*

***Type II respiratory failure (or pump failure) is characterized by decreased $PaO_2$ and increased $PaCO_2$ as a result of alveolar hypoventilation. There is a fall in minute ventilation which causes a rise in $PaCO_2$ and fall in $PaO_2$. The alveolar arterial gradient ($PaO_2$ is normal).***

| Type I Respiratory failure | Type II Respiratory failure |
|---|---|
| Hypoxemia with decreased $PaCO_2$ | Hypoxemia with increased $PaCO_2$ |

**3. Answer is A (Metabolic acidosis with compensatory respiratory alkalosis):** *Harrison 17th/1590; Oxford handbook of Medicine 5th/684*

***With pH < 7.35 (7.12) acidosis is confirmed. Abbnormal $CO_2$ with change in opposite to expected. (acidosis should have increased $CO_2$) indicates that the change in compensatory (compensatory respiratory alkalosis), Decreased bicarbonates with change in keeping with change in pH suggests that the problem is metabolic. Thus the whole picture respresents metabolic acidosis with compensatory respiratory alkalosis.***

**Explanation :**

*Acid base disorders needlessly, confuse many people, but if a few simple rules are applied then interpretation and diagnosis are easy.*

| **pH < 7.35 is acidosis ; pH > 7.45 is alkalosis** |
|---|
| **1° change in $HCO_3^-$ is termed as metabolic** |
| if change in $HCO_3^-$ is in keeping with the pH (i.e. if there is acidosis and $HCO_3^-$ decreased) the problem is a Metabolic one.<br>If change in $HCO_3^-$ is opposite with the pH (if there is acidosis and $HCO_3^-$ is increased or normal)<br>the problem is compensatory metabolic. |
| **1° change is $CO_2$ is termed as respiratory** |
| If change in $CO_2$ is in keeping with the pH (if in acidosis $CO_2$ is raised) the problem is termed respiratory<br>If change in $CO_2$ is opposite with the pH (if there is acidosis and $CO_2$ is decreased or normal)<br>problem is termed as compensatory respiratory. |

**STEP 1 : What is the pH.**

| Normal pH | pH of patient | Inference | Acidosis |
|---|---|---|---|
| 7.35 – 7.45 | 7.12 | pH is decreased | Acidosis |

**STEP II : Is it a metabolic or respiratory change**

| Parameter | Inference | Is change towards acidosis or alkalosis | Is change in keeping with change in pH | Final Inference |
|---|---|---|---|---|
| $pCO_2$ = 18mm Hg (Respiratory component) | $pCO_2$ is decreased | Alkalosis | No | Respiratory component is compensatory |
| $HCO_3$- = 12 mmol/l (Metabolic component) | $HCO_3^-$ is decreased | Acidosis | Yes | Metabolic component is primary |

**STEP III : Final deduction**

*Because metabolic component is primary and respiratory component is compensatory the acid base disorder is Metabolic acidosis with compensatory Respiratory alkalosis.*

4. **Answer is A (Respiratory acidosis with compensatory metabolic alkalosis) :** *Harrison 18th/p 363, 364 Harrison 17th/1590, 288, 289; Read text below*

***Because primary respiratory component is causing acidosis and metabolic component is compensatory by producing alkaosis, the acid base disorder is Respiratory acidosis with compensatory metabolic alkalosis.***

**STEP 1 : What is the pH.**

| Normal pH | pH of patient | Inference | Is it acidosis or alkalosis |
|---|---|---|---|
| 7.35 – 7.45 | 7.2 | Decreased pH | Acidosis |

**STEP II : What component is primary and what is compensatory**

| Parameter | Inference | Is change towards acidosis or alkalosis | Is change in keeping with change in pH | Final Inference |
|---|---|---|---|---|
| $pCO_2$ = 50mm Hg (Respiratory component) | increased | acidosis | Yes (pH=7.2 = Acidosis) | Primary component is respiratory (acidosis) |
| $HCO_3^-$ = 32 mmHg (metabolic component) | increased | Alkalosis | No (pH=7.2 = Acidosis) | Metabolic component is compensatory (alkalotic) |

**STEP III : Final deduction**

*Because the primary component is respiratory and the metabolic component is compensatory the acid base disorder is respiratory acidosis with compensatory metabolic alkalosis.*

5. **Answer is D (Metabolic Acidosis):** *Textbelow; Oxford Hand book of Medicine 5th/684*

***The patient in question has a primary respiratory alkalosis with compensatory metabolic acidosis ($\downarrow HCO_3^-$). Since the question specifically asks about the compensatory mechanism, metabolic acidosis is the single best answer***

***The confusing part in the question is the fact that the primary acid base disorder has not been asked. On the contrary the examiner wants to know the compensatory mechanism involved.The compensatory mechanism here is metabolic acidosis which is the single best answer of choice.***

| PH | Primary Disorder & Parameter | Compensatory mechanism and parameter | Compensatory Mechanism |
|---|---|---|---|
| ↓ed | *Metabolic Acidosis ($\downarrow HCO_3^-$)* | *Respiratory Alkalosis ($\downarrow PCO_2$)* | *Hyperventilation* |
| ↑ed | *Metabolic Alkalosis ($\uparrow HCO_3^-$)* | *Respiratory Acidosis ($\uparrow PCO_2$)* | *Hypoventilation* |
| ↓ed | *Respiratory Acidosis ($\uparrow PCO_2$)* | *Metabolic Alkalosis ($\uparrow HCO_3^-$)* | *$\uparrow HCO_3^-$ reabsorption by kidneys* |
| ↑ed | *Respiratory Alkalosis ($\downarrow PCO_2$)* | *Metabolic Acidosis ($\downarrow HCO_3^-$)* | *$\downarrow HCO_3^-$ reabsorption by kidneys* |

**How we approached the above question : (Refer subsequent explanation)**

*With pH of 7.5 (> 7.45) alkalosis is confirmed as the primary disorder.*
*Since change in $PCO_2$ (↓ed) is in keeping with the change in pH (alkalosis) the primary disorder is Respiratory (Respiratory Alkalosis).*
*Since change in ($\downarrow HCO_3^-$) is opposite with the pH (There is alkalosis and $HCO_3^-$ is reduced), the metabolic component ($HCO_3^-$) is compensatory.*
*The patient therefore has primary Respiratory Alkalosis with Compensatory Metabolic Acidosis*

**Step by Step Approach for such questions**

| |
|---|
| *Remember : Acidosis is inkeeping with Decreased $HCO_3$ and Raised pCO2* |
| *Remember : Alkalosis is inkeeping with Increased $HCO_3$ and Decreased pCO2* |

| |
|---|
| **pH < 7.35 is acidosis ; pH > 7.45 is alkalosis** |
| **1° change in $HCO_3^-$ is termed as metabolic (Normal HCO3- = 22 – 30 meq/l)** |
| if change in $HCO_3^-$ is in keeping with the pH (i.e. if there is acidosis and $HCO_3^-$ decreased) the problem is a Metabolic one.<br>If change in $HCO_3^-$ is opposite with the pH (if there is acidosis and $HCO_3^-$ is increased or normal) the problem is compensatory metabolic. |
| **1° change is $CO_2$ is termed as respiratory (Normal pCO2 = 35 – 45 mmHg)** |
| If change in $CO_2$ is in keeping with the pH (if in acidosis $CO_2$ is raised) the problem is termed respiratory<br>If change in $CO_2$ is opposite with the pH (if there is acidosis and $CO_2$ is decreased or normal) problem is termed as compensatory respiratory. |

**STEP 1 : What is the pH.**

| Normal pH | pH of patient | Inference | Primary disorder (Acidosis/Alkalosis) |
|---|---|---|---|
| 7.35 – 7.45 | 7.5 | pH is increased | Alkalosis |

**STEP II : Is it a metabolic or respiratory change**

| Parameter | Inference | Is change towards acidosis or alkalosis | Is change in keeping with change in pH | Final Inference |
|---|---|---|---|---|
| $pCO_2$ = 30mm Hg (Respiratory component) | $pCO_2$ is decreased | Alkalosis | Yes (pH=7.5 = Alkalosis) | Respiratory component is Primary |
| $HCO_3$- = 18 meq/l (Metabolic component) | $HCO_3^-$ is decreased | Acidosis | No (pH=7.5 = Alkalosis) | Metabolic component is Compensatory |

**STEP III : Final deduction**

*Because Respiratory component is primary and metabolic component is compensatory the acid base disorder in this patient is Primary Respiratory Alkalosis with* ***compensatory Metabolic Acidosis. The compensatory mechanism in this patent therefore is Metabolic Acidosis.***

**6. Answer is C (Respiratory alkalosis):** *Repeat*

*A pH of 7.46 (alkalosis) and a reduced pCO2 (30 mmHg) suggests a diagnosis Respiratory alkalosis.*
***The change in CO2 (alkalosis) is in-keeping with the pH change (alkalosis) thereby suggesting a primary diagnosis of Respiratory alkalosis.***

Rules to acid base disorders: Review

| |
|---|
| **pH < 7.35 is acidosis ; pH > 7.45 is alkalosis** |
| **1° change in $HCO_3^-$ is termed as metabolic (Normal HCO3- = 22 – 30 meq/l)** |
| if change in $HCO_3^-$ is in keeping with the pH (i.e. if there is acidosis and $HCO_3^-$ decreased) the problem is a Metabolic one.<br>If change in $HCO_3^-$ is opposite with the pH (if there is acidosis and $HCO_3^-$ is increased or normal) the problem is compensatory metabolic. |
| **1° change is $CO_2$ is termed as respiratory (Normal pCO2 = 35 – 45 mmHg)** |
| If change in $CO_2$ is in keeping with the pH (if in alkalosis $CO_2$ is reduced) the problem is termed respiratory<br>If change in $CO_2$ is opposite with the pH (if there is alkalosis and $CO_2$ is raised) problem is termed as compensatory respiratory. |

**Stap 1 : What is the pH**

| Normal pH | pH of patient | Inference | Acid / Base disorder |
|---|---|---|---|
| 7.35 – 7.45 | 7.46 | pH is increased | Alkalosis |

**Step II : Is it metabolic or Respiratory**

| $CO_2$ parameter (Normal) | $pCO_2$ of patient | Inference | Is change towards acidosis or alkalosis | Is change in keeping with pH change |
|---|---|---|---|---|
| $pCO_2$ 35-45 mm Hg | 30 mm Hg | $pCO_2$ decreased | Alkalosis | Yes |

***If change in $pCO_2$ is inkeeping with pH (if in alkalosis $pCO_2$ is reduced) the primary acid base abnormality is respiratory.***

*The patient in question thus has primary respiratory alkalosis which may have been partially compensated (data On $HCO_3^-$ values to assess the extent of compensation is not provided in the question).*

7. **Answer is D (Respiratory Alkalosis)**

***The Areterial Blood Gas Analysis suggests a diagnosis of Respiratory Alkalosis.***
A pH of 7.53 (>7.45) suggests confirms Alkalosis. Since the change is in $PCO_2$ (decreased; normal being 35 to 55mmHg) is inkeeping with the change in pH the primary disorder is Respiratory (and not Metabolic). Further the Metabolic component as represented by $HCO_3$ is normal (Normal $HCO_3$ is between 22 to 30 meq/l). The patient therefore has Respiratory Alkalosis.

8. **Answer B (Respiratory acidosis)** *Harrison 18th/p 363, 364 Harrison 17th/1590, 288, 289; Refer previous question*

9. **Answer A (Respiratory alkalosis)** *Harrison 18th/p 363, 364 Harrison 17th/1590, 288, 289;Refer previous questions*

***There is alkalosis (pH = 7.5) and CO2 is low (alkalosis). Change in CO2 is in keeping with change in pH and thus the primary cause is respiratory. The acid base disturbance is thus primary respiratory alkalosis.***

10. **Answer is C (Respiratory and metabolic acidosis)** *Harrison 18th/p363, 364 Harrison 17th/1590, 288, 289; See text below; Refer previous questions*

***The acid base disorder is therefore both respiratory and metabolic acidosis.***

- There is ***acidosis*** (pH < 7.35).
- Raised $PCO_2$ (acidosis) indicates that change in $CO_2$ is in keeping with change in pH. The ***respiratory component is therefore primary***.
- Decreased $HCO_3$ (acidosis) indicates that ***change in $HCO_3$ is also primary***.

*The acid base disorder is therefore both respiratory and metabolic acidosis.*

11. **Answer is B (Non Anion Gap Metabolic Acidosis):** *Refer text below*

***The patient in question has metabolic acidosis with a normal anion gap***

**The Acid base abnormality is Metabolic Acidosis**

*The change in $HCO^3$ (↓) is in keeping with the change in pH (acidosis); therefore the primary acid base abnormality is metabolic (acidosis)*

| Normal pH | pH of patient | Inference | Acid-Base abnormality |
|---|---|---|---|
| 7.35-7.45 | 7.34 | pH is ↓ed | Acidosis |

| Normal Paremeter | Patient Parameter | Deviation | Direction of change | Inkeeping with pH | Final Inference |
|---|---|---|---|---|---|
| $HCO_3^-$ (22-30) | 17 | Decreased | Acidosis | Yes (ph=Acidosis) | Primary mechanism metabolic |
| pCO2 (35-45) | 32 | Decreased | Alkalosis | No (ph=Acidosis) | Compensatory mechanism Respiratory |

***The patient in question therefore has Primary Metabolic Acidosis with Compensatory Respiratory Alkalosis***

**Is this metabolic acidosis associated with a normal or increased Anion Gap**

***Anion Gap is Normal in this case of Metabolic Acidosis*** *(as calculated in the following text)*

| |
|---|
| *Anion Gap is calculated by subtracting the measured anions from cations.*<br>*Anion Gap = (Na+ K+) – ($HCO_3^-$ + Cl)* ***Normal anion gap is about 12-16 meq/l)*** |
| *For the patient in question with $HCO^3$ of 17; $Na^+$ 140; pCO2 32; $K^+$ 4.9; $Cl^-$ 112*<br>*Anion Gap = (140 + 4.9) – (17+112)*<br>*Anion Gap = 15.9* |
| Inference for the patient in question<br>*The anion gap (15.9) is close to the normal range, hence this is a normal anion gap metabolic acidosis* |

**12. Answer is B (Acute exacerbation of COPD):** Refer textbelow

***The patient in question is presenting with type II Respiratory failure (Decreased PaO2 and increased $PaCO_2$) which indicates an obstructive lung disease. Amongst the options provided Asthma and COPD, both are examples of obstructive lung diseases.*** *Obstructive lung disease with elevated $PCO_2$ is more characteristic and common in acute exacerbations of COPD than in Acute Asthma and hence acute exacerbation of COPD is the single best answer of choice.*

| Parameter | Normal | Patient | Inference | |
|---|---|---|---|---|
| pH | 7.38-7.44 | 7.2 | Acidosis | |
| Pco2 | 40 mm/hg | 80mm | Increased | Type II |
| Pco2 | 100 mm/hg | 46mm | Decreased | respiratory failure |

**Acute Asthma and COPD are both examples of Obstructive lung diseases.**

**Both conditions may present with the above picture but an elevated $PCO_2$ is more characteristic of COPD than asthma**

*In acute episodes of Asthma most patients increase total ventilation sufficiently to maintain arterial $PCO_2$ in or below the normal range until a late stage while in cases of COPD persistent elevation of $PCO_2$ is characteristic*

| Disease | $PaO_2$ | $PaCO_2$ |
|---|---|---|
| Acute Exacerbation of COPD | Decreased/Hypoxemia | ***Increased/Hypercarbia*** |
| Acute Episode of Asthma | Decreased/Hypoxemia | ***Normal or Decreased due to hyperventilation***<br>*May be elevated/increase at a late stage when respiratory muscles become tired* |

**ARDS and Pneumonia** are conditions that lead to a primary defect in oxygenation. These are associated with normal or reduced levels of $PaCO_2$ and cause type I respiratory failure

| Disease | $PaO_2$ | $PaCO_2$ |
|---|---|---|
| ARDS | Decreased/Hypoxemia | *Normal or Reduced* |
| Pneumonia | Decreased/Hypoxemia | *Normal or Reduced* |

**13. Answer is B (Ventilatory malfunction) :** *Refer text below*

***Ventilatory malfunction is the single best answer of exclusion***

**The patient has a blood pH of 7.58 indicating alkalosis, decreased oxygen saturation, a low $PCO_2$ and a high $PO_2$.**

| Parameter | Normal | Patient | Inference |
|---|---|---|---|
| pH | 7.38 to 7.44 | 7.58 | Alkalosis |
| $P_{CO2}$ | 35 to 45 mmHg | 23 mmHg | Decreased |
| $P_{O2}$ | 80 to 100 mmHg | 300 mmHg | Increased |
| Oxygen saturation | 97% | 60% | Decreased |

*This is consistent with a diagnosis of ventilatory mal function.*

**None of the other three condition satisfy the given parameters of the patients. The answer of exclusion therefore is some form of ventilatory malfunction.**

- In **carbon monoxide poisoning** ABG analysis would reveal acidosis and normal $PO_2$
- In **voluntary hyperventilation** oxygen saturation would be normal.
- In **methyl alcohol poisoning** ABG would reveal acidosis and not alkalosis.

## Obstructive / Restrictive Pulmonary Diseases

### Pulmonary Function Test

**14. Answer is D (Decreased diffusing capacity) :** *Harrison 18th/ 2092; 15th/ 1448; 16th/ 1500; 17th /1588, 1587, 1637*

*Diffusion capacity is not affected in Obstructive lung diseases [Q] (acute or chronic). It is decreased in restrictive lung disease. [Q]*

- Decreased in expiratory flow rate is a hallmark of obstructive lung disease. (↓MEFR)
- Residual volume is increased & *$FEV_1$/FVC is decreased ($FEV_1$ is also decreased).*

| PFT Result | Obstructive Pattern | Restrictive Pattern |
|---|---|---|
| *$FEV_1$* | ***Decreased (<80% predicted)*** *(Decreased out of proportion to FVC)* | *Decreased (May be preserved)* *(Decreased in proportion to FVC)* |
| *FVC* | *Decreased ( May be preserved)* | ***Decreased (<80% predicted)*** |
| *$FEV_1$/FVC ($FEV_1$%)* | ***Decreased (<0.7)*** | ***Normal or Increased (>0.7)*** |
| *$FEF_{25-75}$* | *<50% predicted* | *Normal / Decreased in proportion to loss of lung volume* |
| *TLC* | *Normal or elevated* | *Decreased* |
| *RV* | *Increased* | *Decreased* |
| *DLCO* | *Normal* *Decreased in Emphysema* | *Decreased in intrinsic restrictive lung disease.* *Normal in neuromuscular or musculoskeletal restrictive disease* |

**$FEV_1$**=forced expiratory volume in one second; **FVC**=Forced Vital Capacity; **$FEF_{25-75}$**=Forced Expiratory Flow at 25%=75% vital capacity; **TLC**= Total Lung Capacity; **DLCO**=Diffusion Capacity of the Lung for Carbon monoxide.

**15. Answer is A (Residual volume Normal):** *Harrison 17th /1588*

***Obstructive Lung disease is typically associated with an Increased Residual volume***

| Disease Pattern | TLC | RV | Vital Capacity | FEV1/FVC | FEF 25-75 |
|---|---|---|---|---|---|
| Obstructive Lung Dusease | N or ↑ed | ↑ed | ↓ed or Normal | ↓ed | ↓ed |

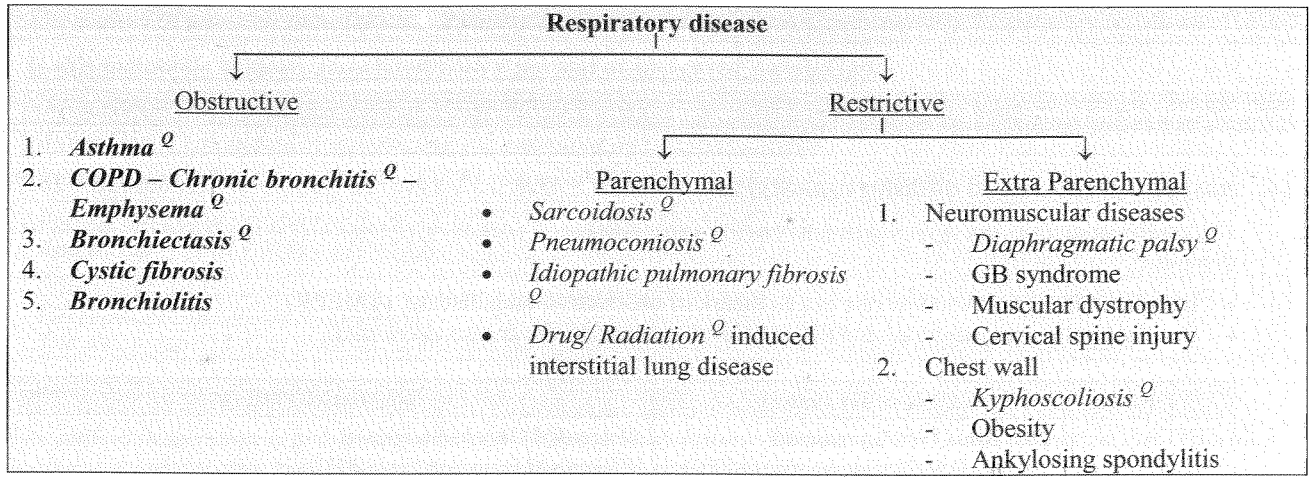
*Taken from Harrison 17th/1588*

**The hallmark of obstructive Lung Disease** is decreased expiratory flow rate such the $FEF_{25-75}$ is reduced and $FEV_1$ is typically reduced out of proportion to the Forced Vital Capacity (↓$FEV_1$/FVC). ***The Residual volume is typically increased***. The vital capacity (FVC) may be normal or decreased while Total Lung capacity may be normal or increased.

**The hallmark of Restrictive Lung Disease** is a decrease in lung volume typically TLC and vital capacity. Flow rates are preserved and hence $FEF_{25-75}$ is generally normal. Also, when $FEV_1$ is considered as a percentage of FVC, ($FEV_1$/ FVC), the flow rates are often supranormal i.e. disporoportionately high relative to the size of lungs. ***Residual volume is also generally decreased***.

**16. Answer is C (Asthma):** *Harrisons 16th/ 1500, 1501; Harrison 17th/1587, 1588, 1589; Harrison 18th/2092*

***Reduction in $FEV_1$/FVC is the hallmark of obstructive lung diseases. Amongst the options provided,*** *Asthma is the only obstructive disease and thus the answer of choice.*




***The hallmark in obstructive pattern of disease is a decrease in expiratory flow rates. Decrease in Forced Expiratory flow rate ($FEF_{25-75}$) and $FEV_1/FVC$ are characteristic.***

**17. Answer is A (Asthma):** *Harrison 18th/2092*

***Decreased FEV1/FVC suggests a diagnosis of Obstructive Lung Disease. Amongst the options provided Asthma is the only condition that leads to Obstructive Pattern of Lung Disease and hence is the answer of choice***
*Kyphosis, Scoliosis and Fibrosis are Restrictive Lung Diseases that are characterized by Normal or Elevated FEV1/FVC ratios.*

**18. Answer is D (↑ ed Residual Volume):** *Repeat*

***Bronchial Asthma presents with an obstructive pattern on Pulmonary function Testing and is associated with an increased Residual volume.***

**19. Answer is D ($FEV_1$/FVC increase and compliance decreases):** *Harrison 15th/ 1449; 16th/ 1500; 17th/ 1588*

***Restrictive lung diseases are characterized by decreased compliance and increased $FEV_1/FVC$***

| $FEV_1$ & FVC | $FEV_1$ / FVC |
|---|---|
| Forced Vital Capacity (FVC) is decreased<br>Forced expiratory flow rates are relatively preserved ($FEV_1$ is preserved) | When $FEV_1$ is considered as a percentage of FVC, the flow rates tend to become supranormal or disproportionately high relative to size of lungs. |
| *$FEV_1$ is preserved and FVC is decreased so $FEV_1/FVC$ is increased* | |

*The hallmark of restrictive lung diseases is a decrease in lung volumes primarily TLC and V.C.' (FVC is decreased)- Harrison*
***Compliance*** *decreases in restrictive lung disease. Compliance is usually unaffected in obstructive lung diseases except in emphysema where it is increased.*

**20. Answer is A (Reduced RV/TLC):** *Harrisons 16th/ 1500, 1501*

***Severe kyphoscoliosis is a restrictive extra-parenchymal disease and presents with decreased RV & decreased TLC on pulmonary function tests.***

| | Obstructive lung disease | Restrictive lung disease |
|---|---|---|
| **Total lung capacity** | ***Normal to Increase Q*** | ***Decrease Q*** |
| **Residual volume** | ***Increase Q*** | ***Decrease Q*** |
| **Vital capacity** | ***Decrease Q***<br>*(May be normal)* | ***Decrease Q*** |
| **$FEV_1$/FVC** | ***Decrease Q (< 0.7)*** | ***Normal to Increase Q (>0.7)*** |
| **FEF 25-75%** | ↓ | ***Normal*** |
| **(Forced expiratory flow rate)** | | |
| **Diffusion capacity** | ***Normal (↓ in emphysema)*** | ***Decreased*** |

**21. Answer is A (Interstitial lung disease):** *Harrison 16th/1500, 1556; 17th/1587-1589, 1643; CMDT 06th/223*

*'Presence of long standing scleroderma together with a 'restrictive pattern' on pulmonary function tests suggests a diagnosis of interstitial lung disease. Interstitial lung diseases produce a restrictive defect. $FEV_1$ and FVC are reduced, but the $FEV_1$/FVC ratio is usually normal or increased.* ***Note that FEV expressed as a percentage is actually $FEV_1$/FVC.*** *Scleroderma or systemic sclerosis is a known cause for interstitial lung disease.*

| PFT | Predicted (normal) | Observed | Interpretation | Inference |
|---|---|---|---|---|
| FVC | 2.82 | 2.63 | ↓ed | Restrictive /Obstructive |
| $FEV_{1\%}$ | 80% | 88% | ↑ed (>80%) | Restrictive |
| DLCO | 16.3 | 5.26 | ↓ed | Restrictive |

| **FVC** |
|---|
| The Forced Vital Capacity (FVC) represents the total volume of gas exhaled with maximum expiration following maximal inspiration. **A reduced FVC suggests pulmonary restriction.** |
| **$FEV_1$% or FEV1/FVC** |
| ***Note that $FEV_1$ exprEssed as a percentage is actually $FEV_1$/FVC.***<br>The volume of gas exhaled during the first second while expiration from FVC is $FEV_1$.<br>$FEV_1$ is often represented as a ratio of the FVC (often referred to as FEV1% rather than $FEV_1$/FVC)-*CMDT'06, p 223*<br>***Normal to increased FEV1% (FEV1/FVC) suggest restrictive lung disease***<br>***Decreased FEV1% ($FEV_1$/FVC) suggests obstructive lung disease.*** |
| **DLCO :** (Diffusion capacity for carbon monoxide) |
| This reflects the ability of lungs to transfer gas across the alveolar - capillary interface.<br>***Decreased DLCO is consistent with a diagnosis of :***<br>• ***Interstitial lung disease***<br>• *Emphysema*<br>• *Pulmonary hypertension* |

| Parameter | Obstructive lung disease | Restrictive lung disease |
|---|---|---|
| **Total lung capacity** | ***Normal to Increase*** $^{Q}$ | ***Decrease*** $^{Q}$ |
| **Residual volume** | ***Increase*** $^{Q}$ | ***Decrease*** $^{Q}$ |
| **Vital capacity** | ***Decrease*** $^{Q}$ *(May be normal)* | ***Decrease*** $^{Q}$ |
| **$FEV_1$/FVC ($FEV_1$%)** | ***Decrease*** $^{Q}$ | ***Normal to Increase*** $^{Q}$ |
| **FEF 25-75%**<br>**(Forced expiratory flow rate)** | ↓ | ***Normal*** |
| **Diffusion capacity** | ***Normal (↓ in emphysema)*** | ***Decreased*** |

**22. Answer is A (Interstitial lung disease):** *Refer previous question; Harrison 16th/1500, 1556; 17th/1587-89,1643; CMDT 6th/223b*

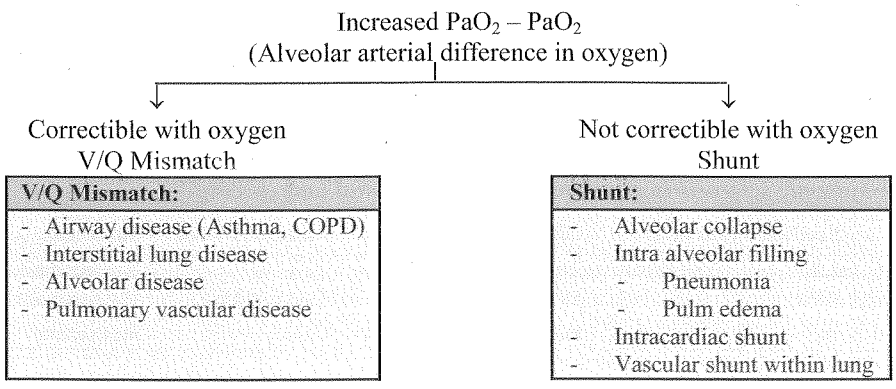
*'Presence of long standing scleroderma together with a 'restrictive pattern' on pulmonary function tests suggests a diagnosis of interstitial lung disease. Interstitial lung diseases produce a restrictive defect. $FEV_1$ and FVC are reduced, but the $FEV_1$/FVC ratio is usually normal or increased.* ***Note that FEV expressed as a percentage is actually $FEV_1$/FVC.*** *Scleroderma or systemic sclerosis is a known cause for interstitial lung disease.*

**23. Answers is B (Sarcoidosis)** : *Harrison 16th / 1500-1501; Harrison 17th/1588, 1589*

*Decreased Vital capacity and Decreased Total Lung Volume suggests a Restrictive Lung Disease picture. Amongst the options provided Sarcoidosis is the only Restrictive Lung Disease and hence the answer of choice.*

**24. Answer is B (Alveolar arterial difference in $PaO_2$):** *Harrison 15th/ 1452; 16th/ 1500, 1504; 17th/ 1588, 1590, 1591*

If the gas exchange at alveolar capillary level occurs normally, the alveolar arterial difference in $PaO_2$ is not elevated. *In infiltrative lung disease the alveolar capillary bed is damaged and there is a decrease in diffusion capacity. This results in an increase in alveolar arterial differences in $PaO_2$.*




**25. Answer is C (Alveolar hemorrhage):** *Harrison 15th/ 1453; 16th/ 1504, 1505; 17th/ 1591, 1592 Harrison 18th/p 2092*

***An elevated $D_{LCO}$ is characteristic of alveolar haemorrhage as in Good pastures syndrome.*** *Hemoglobin contained in erythrocytes in alveolar lumen binds carbon monoxide, so that exhaled CO concentration is diminished and the measured $D_{LCO}$ is increased.*

**Diffusion capacity**

This is measured by estimating $D_{LCO}$ (carbon monoxide diffusion).
It is most useful in assessing disease affecting the
Alveolar capillary bed (interstitial lung disease, emphysema)
Pulmonary vasculature (pulmonary embolism or prim. pul. hypertension)

| Decreased $D_{LCO}$ (Diffusion capacity) | Increased $D_{LCO}$ (Diffusion capacity) |
|---|---|
| 1. **Interstitial lung disease**: scarring of alveolar capillary units diminishes area of alveolar capillary bed as well as pulmonary blood volume<br>2. **Emphysema:** alveolar walls are destroyed so the surface area of alveolar capillary bed is diminished<br>3. **Recurrent pulmonary embolism and Primary pulmonary hypertension:** disease causes a decrease in cross sectional area and volume of pulmonary vasculature | 1. **Alveolar haemorrhage:** as in Good pasture's syndrome: haemoglobin contained in erythrocytes in alveolar lumen binds Co so exhaled carbon monoxide concentration is diminished & $D_{LCO}$ is increased<br>2. **Congestive heart failure:** May be elevated if pulmonary blood volume is increased. Once pulmonary edema ensues $D_{LCO}$ may decrease as and the net $D_{LCO}$ depends on the opposing influences. |

**26. Answer is A (Chronic Bronchitis):** *Harrisons 17th/ 1592 Harrison 18th/p 2092*

***Diffusion capacity for carbon monoxide (DLCO) is usually normal in chronic bronchitis and other obstructive lung diseases with the exception of Emphysema where it is decreased.***

**Diffusion capacity for carbon monoxie** (DLCO)
Diffusion capacity is altered in disease affecting the functional integrity of the alveolar capillary membrane.
In Emphysema, alveolar walls are destroyed, so the *surface area of alveolar–capillary bed is diminished resulting in diminished DLCO.*

Three main categories are associated with lowered DLCO

- *Emphysema* Q
- *Interstitial Lung Disease* Q
- *Pulmonary vascular disease (Recurrent Pulmonary emboli or Primary Pulmonary Hypertension)* Q

**27. Answer is A (Small airways):** *Harrison 15th/ 1446, 1448; Harrisons 16th/ 1500; Harrison 17th/ 1588*

***Maximum mid-expiratory flow rate (MMFR)*** **is the average expiratory flow rate during the middle 50% of the vital capacity, i.e. forced expiratory flow rate between 25 and 75% of the vital capacity.**
***MEFR is considered a more sensitive measurement of early airflow obstruction particularly in small airways.***
*'With obstructive disease only in the small airways, the only abnormality noted on routine testing of pulmonary function may be a depression in $FEF_{25-75}$ and an abnormal terminal portion of forced expiratory flow volume curve. $FEV_1/FVC$ may be normal' – Harrisons.*

## Bronchial Asthma

**28. Answer is D (IgE is increased in Extrinsic Asthma):** *Harrisons 17th/1596, Clinical Anaesthesiology by Morgan 4th/573 Harrison 18th/p 2102*

***Idiosyncratic Asthma (Intrinsic Asthma) is associated with normal IgE levels.***

**Asthma**

| Extrinsic Asthma / Allergic Asthma | Intrinsic Asthma /Idiosyncratic Asthma |
|---|---|
| • History of Atopy is present | • No history of Atopy (Concomitant nasal polyps are usually present and patients may be aspirin sensitive) |
| • Attacks related to environmental exposures | • Attacks not related to environmental exposures: Occur without provocation |
| • IgE antibody levels are ↑ ed | • IgE antibody levels are normal |
| • Early onset of disease (young) | • Delayed onset of disease (Adult onset Asthma) |
| • Usually is less severe, intermittent Asthma that may however progress to severe persistent Asthma | • Usually have more severe persistent Asthma |

**The incidence of Asthma is increasing**

*There is a rising incidence of Asthma in developing countries – Harrisons 17th/1596*

**29. Answer is C, E (Family history +ve; Allergic in nature):** *Harrison 17th/1596 Harrison 18th/p 2102*

***Intrinsic Asthma by defination is not allergic in nature and is not associated with a positive family history of allergy***

**Features of Intrinsic Asthma**
*(Nonatopic asthma- Approximately 10% of asthmatic patients are intrinsic )*

- ***Negative Family History of allergy***
- ***Negative skin test to common inhalant allergens (Not primarily caused by allergy)***
- *Normal serum concentration of IgE.*
- *Concomitant nasal polyps (Common)*
- *Sensitivity to aspirin and related chemicals*
- *Later onset of disease (adult-onset asthma)*
- *More servere, persistent disease/asthma.*

**30. Answer is C (Nasal Polyp) :** *Refer previous question*

***Aspirin Sensitive Asthma or Intrinsic Asthma is a non-atopic idiosyncratic form of asthma typically associated with concomitant nasal polyps.***

**31. Answer is C (Nasal polyp):** *Harrison's 14th/ 1421; Harrison's 15th/ 1458; 16th/ 1510; 17th/ 1596, 1606 Harrison 18th/p 2102, 2115*

*'Aspirin associated Asthma usually begins with perennial vasomotor rhinitis that is followed by a hyperplastic rhinosinusitis with nasal polyps' – Harrisons*

**Aspirin associated Asthma:**

- Primarily affects adults, although the condition may occur in childhood.
- Usually begins with perennial vasomotor rhinitis that is followed by hyperplastic rhinosinusitis with nasal polyps. Progressive asthma then appears.
- On exposure to even very small quantities of aspirin affected individual typically develop ocular and nasal congestion and acute, often severe episodes of airways obstruction.
- Death may follow ingestion of aspirin.

**32. Answer is C (Hyporesponsiveness of airway):** *CMDT 2008 / 206; 2009/210; Harrisons 17th/1598, 1601, 1603 Harrison 18th/p 2104, 2108, 2111*

***Asthma is characterized by Hyperresponsiveness of airways and not hyporesponsivenes***

**Asthma is an inflammatory disorder of the airways**
*Asthma is a chronic inflammatory disorder of the airways – CMDT-2009/210*

**Asthma is an allergic disease of the airways**
*The pattern of inflammation in Asthma is characteristic of allergic disease' – Harrison 17th/1598*
The strongest identifiable predisposing factor for Asthma is Atopy.
*Exposure of sensitive patients to **'allergans'** increases airway inflammation airway hyper responsiveness and symptoms - CMDT 2009/210*

**Asthma is associated with hyper responsiveness of airways (AHR)**
*Airway hyperresponsiveness (AHR) is the characteristic physiologic abnormality of Asthma*

*AHR describes the excessive bronchoconstricter response to multiple inhaled triggers that would have no effect on normal airways- Harrison 17th/1601*

**Inhaled corticosteroids are the mainstay of treatment**
*Inhaled corticosteroids are by far the most effective controllers for Asthma and their early use has revolutionized asthma therapy.*
*Inhaled corticosteroids are now given as first line therapy to patients with persistent Asthma - Harrisons 17th/1603*

**33. Answer is D (Small airways are not involved):** *Refernces alongwith text*

***Asthma involves both large and small airways but alveoli are not involved***

**Charcot Leyden crystals may be seen in sputum:** *Robbins 7th/726 Pathology by woolf 1st (1998)/434*

Sputum from Asthmatics show certain characteristic features, including charcot leydencrystas

| The microscopically identifiable features described in sputum are three 'C's | |
|---|---|
| *Charcot Leyden crystals* | *: Derived from granules of eosnophils and found only in Asthma* |
| *Curshmann spirals* | *: Curiously twisted casts of airways : Whorls of shed epethelium* |
| *Creola bodies* | *: Clumps of cells or isolated metaplastic cells* |

**Reversible Airflow obstruction is a charachteristic feature** (Davidsons 18th/55, 326)
*Reversible Bronchoconstriction is the hallmark of Asthma*
*The charachteristic feature of Asthma is Intermittent and Reversible airflow obstruction.*
*Narrowing of airways is usually reversible, but in some patients with chronic asthma there may be an element of irreversible air flow obstruction*

**Asthma involves both large and small airways**
*Asthma involves Large and small airways but not alveoli - 'Allergic Diseases: Diagnosis Treatment' 3rd/ 120*
*The large and small airways are both involved in Asthma - 'Childhood Asthma: Diagnosis, Treatment & Management' 1st/15*

**Intermittent Asthma responds better to bronchodilator therapy than persistant Asthma**
Bronchodilators are effective drugs for the treatment of acute exacerbations or intermittent episodes of Asthma but they are not sufficient to control asthma in patients with persistant symptoms (persistant asthma)
*'Bronchodilators are not sufficient to control Asthma in patients with persistant symptoms' – Harrisons 17th/1602*

**34. Answer is C (Necrosis of airways):** *Harrison 18th/p 2107 Harrisons 17th/1600*

***Necrosis of Airways is not a feature of Bronchial Asthma***

Features of Asthma: Chronic inflammatory disorder

- ***Chronic inflammatory disorder***
- ***Hyperresponsiveness of airways (AHR)***
- *Airway epithelial shedding*
- *Subepithelial fibrosis and thickening of basement membrane*
- *Hypertrophy and Hyperplasia of airway smooth muscle*
- *Increased mucosal blood flow (vascular congestion)*

- *Microvascular leakage resulting in **airway edema** and plasma exudation into airway lumen*
- ***Mucus Hypersecretion** and formation of viscid mucus plugs that occlude airways*
- *Airway remodelling*
- *Defects in autonomic neural control*

**35. Answer is E (None: All are Features of Acute severe Asthma) :** *CMDT 2008/207; 2009/211*

***Tachycardia (HR>120/min). PEFR < 50%, Pulsus paradoxus and Respiratory Acidosis are all features of Acute severe Asthma.***

**Classification of severity of asthma execrbations:**

| | Mild | Moderate | Severe | Impending Respiratory Failure |
|---|---|---|---|---|
| ***Symptoms*** | | | | |
| Breathlessness | With activity | With talking | At rest | At rest |
| Speech | Sentences | Phrases | Words | Mute |
| ***Signs*** | | | | |
| Body position | Able to recline | Prefers sitting | Unable to recline | Unable to recline |
| Respiratory rate | Increased | Increased | Often > 30/min | > 30/min |
| Use of accessory respiratory muscle | Usually not | Commonly | Usually | Paradoxical thoracoabdominal movement |
| Breath sounds | Moderate wheezing at mid-to-end-expiration | Loud wheezes throughout expiration | Loud inspiratory and expiratory wheezes | Little air movement without wheezes |
| ***Hear rate (beats/min)*** | <100 | 100-120 | ***>120*** | Relative bradycardia |
| ***Pulsus paradoxus*** (mm Hg) | < 10 | 10-25 | ***Often > 25*** | Often absent |
| Mental status | May be agitated | Usually agitated | Usually agitated | Confused or drowsy |
| Functional assessment | | | | |
| ***PEF (% predicted )*** | > 80 | 50-80 | ***< 50*** | < 50 |
| $Sao_2$ (%, room air) | > 95 | 91-95 | < 91 | < 91 |
| $Pao_2$ (mm Hg, room air) | Normal | > 60 | < 60 | <60 |
| $Paco_2$ (mm Hg) | < 42 | < 42 | ≥ 42 ***(Respiratory acidosis)*** | ≥ 42 |

**36. Answer is C (Grave Prognosis):** *'CMDT 2013; Branchial Asthma' by Gershin (Springer) 2012/181*

***Silent chest (Little/no air movement without wheezes in Bronchial Asthma suggests a grave prognosis/ impending respiratory failure (Life threatening Asthma).***

*'Signs of impending respiratory failure include drowsiness or confusion, diaphoresis, bradycardia, paradoxical thoracoabdominal movement **and a silent chest** and should prompt preparation for intubation and mechanical ventilation' - 'Bronchial Asthma' (Springer) 2012/181*

*'Features of life threatening asthma that indicate respiratory failure (impending arrest) include confusion and drowsiness, **silent chest**, PEFR < 33% predicted, paradoxical thoracoabdominal excursions (outward abdominal and inward chest movement during inspiration), bradycardia, hypotension, pulsus paradoxus and hypercapnea (hypoxemia)'- Acute & Critical Care Medicine at a Glance' by Leach (John Wiley & Sons) 2010/75*

**37. Answer is C (Moderate Persistent Asthma):** *Expert Pannel Report–3 (EPR-3): 'Giudelines for the diagnosis and management of Asthma' Summary Report 2007 (NIH Publication Number 08-5846); Koda-Kimble and Young's Applied Therapeutics: The Clinical Use of Drugs 10TH/568,569,570*

***Moderate Persistent Asthma in an adult (>12 years) is defined as Day-Time Symptoms that occur daily and Night-Time Symptoms occurring more than 1 night per week but not every night.***

***Classification of Asthma in Adults >12 years of Age***

| ***Component of Severity*** | ***Intermittent*** | ***Persistent*** | | |
|---|---|---|---|---|
| | | ***Mild*** | ***Moderate*** | ***Severe*** |
| ***Symptoms*** | *≤ 2 days/week* | *> 2 days/week but not daily* | *Daily* | *Throughout the day* |
| ***Night-time Awakenings*** | *≤ 2x/month* | *3–4x/month* | *> 1x/week but not nightly* | *Often 7x/week* |

**38. Answer is A (Hypoxia):** *Harrison 18th/ 2109; Harrisons 11th/1062 (Not elaborated in new edition.)*

***Hypoxia is a universal finding during acute exacerbation's*** *– Harrisons 11th/1062*

*Hypoxia is a universal finding during acute exacerbations. Most Asthmatics have hypocapnia and respiratory alkalosis.*
*- Harrison*

**Hypoxia** is the universal finding in Asthma

**Hypocapnia and respiratory alkalosis** is seen in most asthmatic patients

**Hypercarbia and Respiratory acidosis** *are very late features of Asthma and signify severe obstruction and respiratory failure. These are not universal findings in Asthma.*

**Metabolic acidosis** *is not a feature of Asthma.*

**39. Answer is C (Diurnal variation in PEF > 20 Percent):** *Clinical Asthma: Theory and Practice (CRC Press, 2014)/67; Textbook of Pulmonary and Critical Care Medicine (JP Medical Ltd, 2011)/879,880; Harrison 18th/ 2109*

***Demonstrate Outflow Obstruction***
*Decreased FEV1*
*Decreased PEF*
*Decreased FEV1/FVC*

*While respiratory symptoms suggest asthma, the sine qua non for the diagnosis of asthma is the presence of Reversible Airflow Obstruction and/or Airway Hyper-responsiveness or Increased Peak Expiratory Flow (PEF) Variability in subjects without airways obstruction.*

| *Reversible Airflow Obstruction* | *Increased Peak Expiratory Flow Rate (PEF) Variability* | *Airway Hyper-responsiveness* |
|---|---|---|
| • *Reversibility is demonstrated by repeating spirometry results 15 minutes after administering a short acting bronchodilator*<br>*>12% reversibility in FEV1*<br>*>200 ml increase in Baseline FEV1*<br>• *Positive Reversibility Results Strongly suggest a diagnosis of Asthma (Considered Diagnostic)* | • *Demonstration of Diurnal Variation in the Peak Expiratory Flow Rate*<br>• *A diurnal variation in PEF of more than 20 percent Strongly suggests a diagnosis of Asthma (Considered Diagnostic)* | • *Measured by Methacholine or Histamine challenge.*<br>*Increasing Concentrations of Methacholine are administered and if the FEV1 drops to >20 percent of baseline with any standard dose the test is considered positive.*<br>• *Positive test strongly suggests a diagnosis of Asthma* |

**40. Answer is A (Asthma)**

***An obstructive pattern of PFTs with reduction in the ratio of FEV1; FVC along with demonstration of reversibility of airway obstruction (> 200 ml increase in baseline FEV1) after bronchodilator administration is typical of Asthma.***

**Evidence of airway obstruction can be made with PFTs.**

When airway obstruction is present, the values of $FEV_1$ and FVC can both be reduced.
But $FEV_1$ is disproportionately reduced compared to FVC, thereby giving a lower $FEV_1$; FVC ratio.
The primary criterion for the diagnosis of obstruction is reduction in $FEV_1$/FVC Ratio

| *Asthma* | *COPD (Chronic Bronchitis/Bronchiectasis/Emphysema)* |
|---|---|
| • *In asthma, there is an obstructive pattern of PFT s with reduction in the ratio of FEV1; FVC but this obstruction is typically reversible after bronchodilator administration.*<br>• *This can be demonstrated on spirometry by the measurement of FEV1 and FVC before and after the administration of bronchodilators.*<br>• *Reversibility of > 12% of FEV1 (Or 200ml increase from baseline) supports a diagnosis of asthma.*<br>*The primary functional abnormality is the presence of reversible airway obstruction. However, the absence of improvement after bronchodilator treatment does not exclude reversible obstruction. Obstruction may be due to inflammation. This may only be reversible after prolonged anti-inflammatory therapy.* | • *In chronic obstructive pulmonary disease (COPD)/emphysema there is an obstructive pattern of PFT s with reduction in the ratio of FEV1; FVC, but this obstruction is usually not responsive to bronchodilator administration.*<br>• *In contrast to asthma, the diffusion capacity of the lung for carbon monoxide (DLCO) is often reduced in Emphysema.*<br>• *In advanced disease once air trapping becomes more evident-the total lung capacity (TLC) and residual volume (RV) increase, resulting in an increase in the RV/TLC ratio.* |

*Note:*
*In the face of borderline FEV1; FVC, earlier airflow obstruction may be occasionally be detected by forced expiratory flow (FEF) 25-75%. The rationale being that earlier changes in airway obstruction start in the smaller and peripheral airways. This is a nonspecific finding and should not be used as a criterion for the diagnosis of small airways disease.*

**41. Answer is D (Demonstration of Reversible obstruction):** *Harrison 18th/p 2109 Harrisons 17th/ 1602*

***The diagnosis of asthma is usually apparent from the symptoms (Wheezing, dyspnea, cough) but is confirmed by objective measurement of lung function and demonstration of reversibility.***

Wheezing, Dyspnea, cough
↓
Suspect Bronchial Asthma
↓
Perform PFT to show obstructive pattern
FEV : ↓ed
FEV1/ FVC < 0.7
↓
Demonstrate Reversibility
>12% or 200 ml increase in $FEV_1$ 15 minutes after an inhaled $B_2$ agonist

**42. Answer is A and C (Fluticasone and Budesonide):** *Ref. Text below*

***Fluticasone and Budesonide are inhaled corticosteroids and potent anti-inflammatory medications in Asthma.***

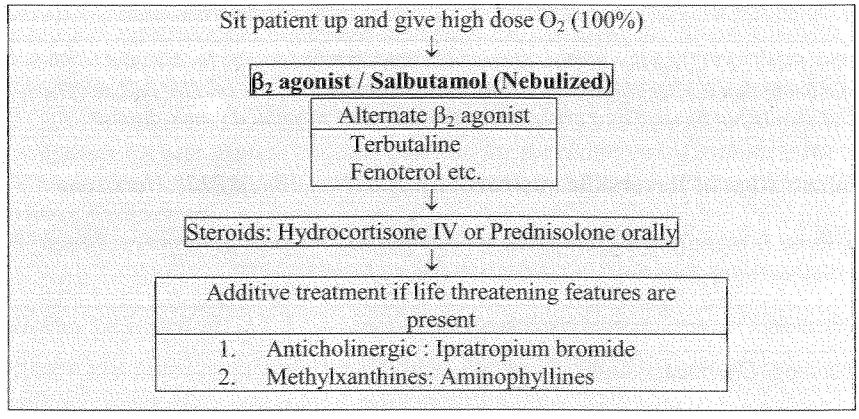
Medications in Bronchial Asthma

| Bronchodilators | Anti-inflammatory (Controllers) |
|---|---|
| Beta 2 Sympathomimetics | Corticosteroids (Inhalational) |
| • *Salbutamol* | • *Beclomethasone* |
| • *Terbutaline* | • *Budesunide* |
| • *Bambuterol* | • *Fluticasone* |
| • *Salmeterol* | • *Flunisolide* |
| • *Formeterol* | • *Ciclesonide* |
| • *Ephedrine* | Corticosteroids (systemic) |
| Methylxonthines | • *Prednisolone, Hydrocortisone e/c* |
| • *Theophylline* | Mast cell stabilizers |
| • *Aminophylline* | • *Sodium cromoglycate (Nedoevil sodium)* |
| Articholinergics | • *Ketotifen* |
| • *Ipratropium bromide* | Leukotriene antogonist |
| • *Tiotropium bromide* | • *Montelukast* |
| | • *Zafirlukast etc* |

**43. Answer is B (Morphine):** *Harrison 17th/ 1605; KDT 5th/ 423*

***Morphine is contraindicated in asthma because it causes constriction of bronchial muscle by causing histamine release.***

**Management of Acute Bronchial Asthma:**




**44. Answer is D (Morphine):** *Refer text below; Repeat*

***Morphine is not used in the treatment of Bronchial Asthma.***
*Bronchodilators (Salbutamol; Aminophylline) and Corticosteroids (Systemic/inhalational) form the mainstay for treatment of Bronchial Asthma.*

**45. Answer is C (Montelukast):** *Harrison's 16th/1514; 17th/ 1602-1604; 18th/2110-2112 CMDT 2009/222; 2008/210-213*

***'Leukotriene modifiers (eg. Monteleukast, Zafirulukast) may be considered as alternatives to low dose inhaled corticosteroids in patients with mild persistent asthma'*** *– CMDT*
*They have no role in aborting an attack of acute severe asthma.*

**46. Answer is A (May be used for acute asthma):** *Harrison's 16th/ 1514; 17th/ 1604; 18th/2112; CMDT 2009/ 222; 2008/212*

*Leukotriene modifiers have no role in aborting an attack of bronchial Asthma.*

**Leukotriene Modifiers:**

These are new group of agents used for asthma and act by modifying the role of leukotrienes which are critical in the pathway of generating features of asthma.

| **Action** | |
|---|---|
| Leukotrienes are responsible for many of the critical elements of asthma<br>Leukotriene modifiers act by two mechanisms to disable the deleterious effects of leukotrenes | |
| Reduce synthesis of all Leukotrienes by inhibiting enzyme involved in their formation i.e. 5 Lipooxygenase | Competitive blockage of principal leukotriene (LTD 4) |
| Zileuton | Montelukast or Zafirulukast |
| **Uses** | |
| 1. Used as alternative to low dose inhaled corticosteroids in patients with mild persistent asthma<br>- reduces asthma morbidity<br>- diminishes nocturnal symptoms<br>2. Used for protection against exercise induced Asthma. | |
| **Side effects:** Leukotriene blockers have been associated with Churg-Strauss Syndrome [Q] | |

**47. Answer is A (Omalizumab):** *Harrison 18th/ 2112*

***Omalizumab is a recombinant IgE Antibody approved for use in treatment of moderate and severe persistent asthma***

***Omalizumab*** *is a recombinant IgE blocking antibody that neutralizes circulating IgE. It prevents circulating IgE from binding to receptors on the surface of Basophils and Mast cells and thus inhibits IgE mediated reactions. Omalizumab is indicated for treatment of 'moderate to severe' persistent asthma in patients who react to perennial allergens (Allergic Asthma). Treatment with Omalizumab has shown to reduce the number of exacerbations in patients with severe asthma and may improve asthma control. However this treatment is very expensive and is only suitable for highly selected patients who are not controlled on maximal doses of inhaler therapy and have a high circulating IgE (within a specified range). Omalizumab is usually given as a subcutaneous injection for 2 to 4 weeks and may be used in adults and adolescents more than 12 years of age.*

| *Omalizumab does not bind to cell bound IgE* |
|---|

**48. Answer is B (Acute Asthmatic Attack):** *KDT 5th/ 127, 4th/ 141; KDT 5th / 1207*

***"Propanalol worsens chronic obstructive lung disease. It can precipitate life threatening attack of Bronchial Asthma as it increases Bronchial resistance by Blocking $_2$ receptors"*** *– KDT*

| Drugs most commonly associated with the induction of acute episodes of Asthma |
|---|
| 1. Aspirin [Q] |
| 2. Beta adrenergic blockers [Q] |
| 3. Colouring agents such as tartrazine |
| 4. Sulfiting agents. |

**49. Answer is A (< 5 μ):** *Harrison 18th/p 2122; Harrison 14th/ 1489, 15th/ 1530; 17th/ 1612;*

***'Particles of size < 2.5 mm can be carried to the lower airways.***

- *'Particles with size above 10-15 mm in diameter, because of their settling velocities in air, do not penetrate beyond the upper airways'*
- *'Particle of size 2.5-10 mm deposit relatively high in the tracheobronchial tree.'*
- *'Particles of size < 2.5 mm can be carried to the lower airways.'*

## Chronic Bronchitis

**50. Answer is A (Chronic Bronchitis):** *Robbins 8th/668; Bail and Hammer's Pulmonary pathology 3rd/866*

***Reid Index is a measure of hypertrophy of the mucus secreting glands and is characteristically increased in Chronic Bronchitis.***

**Reid Index: Measures Hypertrophy of mucus glands**

- Chronic Bronchitis is assoicated with hypertrophy of the mucus secreting glands of the submucusa in the cartilaginous airways.
  - *The histologic correlate of chronic bronchitis is the presence of mucus gland hyperplasia.*
- This manifests as an increased percentage of bronchial wall occupied by submucosal mucus glands (*This is classically defined by the 'Reid Index'.*)
- ***Reid Index is the ratio of the thickness of the mucous gland layer to the thickness of the bronchial wall*** (between basal lamina of mucosa and inner perichondrium)
- *The normal Reid Index is less than 0.4*
  - *Reid index > 0.4 (typically > 0.5) suggests mucous gland hyperplasia*
- The Reid index is increased in chronic bronchitis usually in proportion to the severity and duration of disease.
  - *There is a direct correlation between the value of Reid Index and the volume of daily sputum production by the patient.*

**51. Answer is D (Staphylococcus aureus):** *The Global Initiative for Chronic Obstructive Lung Disease (GOLD); Report produced by the National Heart, Lung, and Blood Institute (NHLBI) and the World Health Organization (WHO)*

***Staphylococcus Aureus is not a common bacterial pathogen responsible for Acute Exacerbation of Chronic Bronchitis.***

**Common Bacterial Pathogens (30%-50%) Responsible for Acute Exacerbations of COPD**

- Haemophilus influenza
- Streptococcus pneumonia
- Moraxella catarrhalis

*Pseudomonas aeruginosa and Enterobacteriaceae are also commonly isolated, particularly from patients with severe COPD.*

**Acute Exacerbation of COPD: Bacterial Infections**

- The GOLD, the NHLBI and the WHO, defines exacerbation of COPD as acute increase in symptoms beyond normal day-to-day variation. This generally includes one or more of the following cardinal symptoms.
  - Cough increases in frequency and severity
  - Sputum production increases in volume and/or changes character
  - Dyspnea increases
- Constitutional symptoms, decrease in pulmonary function, and tachypnea are variably present during an exacerbation, but the CXR is usually unchanged. In the presence of severe underlying airflow obstruction, exacerbation can cause respiratory failure and death.
- It is estimated that 70 to 80% of exacerbations of COPD are due to respiratory infections. The remaining 20 to 30% are due to environmental pollution or have an unknown etiology. Viral and bacterial infections cause most exacerbations
- Bacterial infections appear to trigger 33% to 50% of COPD exacerbations.
- Non-typeable H. influenzae, M. catarrhalis, and S. pneumoniae are the bacteria most frequently isolated bronchoscopically from patients having an exacerbation of COPD
- Pseudomonas aeruginosa and other members of family Enterobacteriaceae are also commonly isolated, particularly from patients with severe COPD.
- Exacerbations of COPD are strongly associated with acquisition of new strain of H. influenzae, M. catarrhalis, S. pneumoniae, or P. aeruginosa. As a result, it has been proposed that acquisition of new bacterial strain plays central role in the pathogenesis of an exacerbation. The idea that exacerbations of COPD are due to acquisition of new strain of bacteria has largely replaced older hypothesis that increases in concentration of colonizing bacteria are the primary cause of exacerbations.

## Emphysema

**52. Answer is B (Panacinar emphysema):** *Robbins 5th/685; Robbins 7th/718*

***Panacinar emphysema is associated with $\alpha_1$ antitrypsin deficiency.*** *– Robbins 7th/ 718*

**There are two types of emphysema that cause clinically significant airflow obstruction:**

| Panacinar emphysema | Centriacinar emphysema |
|---|---|
| • Acini are uniformly involved from level of respiratory bronchiole to terminal blind alveoli. ♀<br>• Lesions are more common in lower zone and bases ♀<br>• Occurs in association with $\alpha_1$ antitrypsin deficiency ♀ | • Central or proximal parts of acini formed by respiratory bronchioles are affected whereas distal alveoli are spared♀<br>• Lesions are more severe and common in Upper lobes ♀<br>• Occurs predominantly in smokers ♀<br>• Is the commonest pattern ♀ |

**53. Answer is C (Restrictive pattern on pulmonary function test is seen):** *Harrison 18th/2156 Harrisons 17th/1640 CMDT 2008/219; 09/230*

***The hallmark of Emphysema is air flow obstruction and pulmonary function tests show an obstructive pattern***

**Breathlessness (Dyspnea) is a charachteristic presenting symptom**
*The three most common symptoms in COPD (emphysema) are cough, sputum production and* ***exertional dyspnea***

**Obstructive (and not Restrictive) pattern is seen on PFT**
*The hallmark of Emphysema (COPD) is airflow obstruction.*
*PFT shows airflow obstruction with a reduction in $FEV_1/FVC$ (< 0.7)*

**Diffusion of carbon monoxide is Reduced (↓DLCO)**

Three main categories of disease with Reduced DLCO are:
*Interstial Lung disease*
***Emphysema***
*Pulmonary vascular Disease*

**Long term bronchodilater therapy does not improve lung function**

*'Bronchodilators do not alter the inexorable decline in lung function that is a hallmark of the disease' -CMDT 2008/219*

*The only drug therapy that is documented to improve the natural history (lung function) of COPD patients is supplemental oxygen in those patients with resting hypoxemia -CMDT 09/230*

The only three interventions that influence the natural history of COPD patients
*Smoking cessation*
*Oxygen therapy in chronically hypoxemic patients*
*Lung volume reduction surgery in selected patients with emphysema*

**54. Answer is B (Increased diffusion capacity for carbon monoxide (DLCO)):** *Harrison 18th/2092; 17th/1592*

***Emphysema is associated with a decreased diffusion capacity for carbon monoxide***

| Lung Function Tests in Emphysema | | |
|---|---|---|
| *TLC* | : | *Normal or Increased* |
| *$FEV_1$* | : | *Decreased (< 80% predicted) (Decreased out of proportion to FVC)* |
| *FVC* | : | *Decreased* |
| *FEV1 / FVC* | : | *Decreased (< 0.7)* |
| *$FEF_{25-75}$* | : | *Decreased (<50% predicted)* |
| *DLCO* | : | *Decreased* |

*Note that DLCO is normal in other obstructive lung diseases like chronic bronchitis*

**Diffusion capacity for carbon monoxie** (DLCO)
Diffusion capacity is altered in disease affecting the functional integrity of the alveolar capillary membrane.
In Emphysema, alveolar walls are destroyed, so the *surface area of alveolar–capillary bed is diminished resulting in diminished DLCO.*

Three main disoders are associated with lowerd DLCO

- *Emphysema* [Q]
- *Interstitial Lung Disease* [Q]
- *Pulmonary vascular disease (Recurrent Pulmonary emboli or Primary Pulmonary Hypertension)* [Q]

**55. Answer is A (Body Plethysmography):** *Harrison's 7th/1587; Pulmonary / Respiratory Therapy Secrets 2nd/45*

***Body Plethysmography is the investigation of choice for estimating lung volumes in the setting of COPD with bullous lesions (trapped air)***

Estimating Lung Volumes

| **Gas Dilution Technique** *(Helium / Nitrogen Dilution Method)* | **Body Plethysmography** |
|---|---|
| • Gas dilution methods are *fairly accurate in measurement of lung volumes in restrictive lung diseases*, but *not so in obstructive lung diseases with trapped air in bullae*. | • Body Plethysmography is *fairly accurate in measurement of lung volumes in both restrictive lung diseases and obstructive lung diseases even with trapped air in bullae* |
| • *Gas dilution methods tend to under-estimate lung volumes in patients with emphysema with ballous lesions as they do not measure the volume of trapped gas or bullae.* | • *Body Plethysmography also measures the volume of any gas containing space in the thorax, including bullae.* |

*The difference between Lung volume measurements by Body Plethysmography and gas dilution technique reflects the amount of gas trapped in bullae.*

## Bronchiectasis

**56. Answer is B (Cystic Fibrosis):** *Clinically Oriented Pulmonary Imaging (Springer Science & Business Media), 2012/187; Thoracic Imaging: Pulmonary and Cardiovascular Radiology (Lippincott Williams & Wilkins, 07-Dec-2011) 2nd/585*

***Bilateral upper lobe bronchiectasis suggests a diagnosis of Cystic Fibrosis.***
*Bilateral upper lobe bronchiectasis is seen most commonly in patients with Cystic Fibrosis and Allergic Bronchopulmonary Aspergillosis (ABPA).* ***Unilateral Upper Lobe Bronchiectasis is seen most commonly in patients with Tuberculosis.***

*Cystic Fibrosis (CF) has a tendency to involve both upper lobes (Upper lobe predominance) although all lobes may be involved. Bronchiectasis in CF usually has a bilateral, proximal, parahilar (central) and upper lobe predominance.* ***Tuberculosis also has a tendency to involve upper lobes but it is more often unilateral than bilateral.*** *Bilateral upper lobe bronchiectasis may however also be seen in Tuberculosis*

**General rules for distinguishing between different causes of bronchiectasis**
*Thoracic Imaging: Pulmonary and Cardiovascular Radiology (Lippincott Williams & Wilkins, 07-Dec-2011) 2nd/585*

- ***Unilateral upper lobe bronchiectasis is most common in patients with Tuberculosis***
- ***Bilateral upper lobe bronchiectasis is seen most commonly in patients with CF and ABPA***
- Central bronchiectasis is more common in patients with ABPA and CF

- Severe and extensive bronchiectasis is most common in patients with ABPA and CF
- Middle lobe and Lingular bronchiectasis suggests MAC (Mycobacterum Avium Intracellulare) infection.
- Lower lobe bronchiectasis is most typical of childhood infections and syndromes associated with impaired mucociliary clearance or immunodeficiency
- Lobar bronchiectasis suggests infection or bronchial obstruction

**57. Answer is D (Left lower lobe):** *API Medicine 6th/ 236, API 7th/ 306*

*"Bronchiectasis is commonly affects lower lobe bronchi, the left side being affected more frequently than right"* – *API 7th*

*Right middle lobe and lingual are next in frequency of involvement.*

**58. Answer is A (Tuberculosis):** *CMDT 2014/279; Manual of Practical Medicine 5th/370; Clinical Tuberculosis by Davies and Gordon (CRC Press) 5th/ 136*

***Bronchiectasis Sicca or Dry Bronchiectasis is typically associated with Tuberculosis***

Tuberculosis is associated with a type of dry bronchiectasis called Bronchiectasis Sicca, which is predominantly seen in upper lobes. Dry Bronchiectasis (Bronchiectasis Sicca) is typically characterized by absence of copious amount of sputum which is usually a hall mark of bronchiectasis. Dry cough associated with hemoptysis is the typical presentation.

**59. Answer is B (Middle Lobe Bronchiectasis):** *Manual of Practical Medicine 5th/370; Clinical Tuberculosis by Davies and Gordon (CRC Press) 5th/ 136*

***Brock's syndrome or middle lobe syndrome refers to Right middle lobe bronchiectasis typically occurring as a late sequel of primary tuberculosis.***

| **Brock's Syndrome** |
|---|
| Right middle lobe bronchiectasis occurring as a late sequel of primary tuberculosis is known as Brock's syndrome or middle lobe syndrome. Brock's syndrome is believed to be caused by pressure of lymph nodes in primary tuberculosis on the middle lobe bronchus. It has been described as a typical outcome of hilar node involvement by tuberculosis in childhood. This term is also applied to recurrent atelectasis of the right middle lobe in the absence of endobronchial obstruction. Bronchiectasis develops after recurrent episodes of atelectasis and fibrosis |

**60. Answer is B (Lung cancer):** *API 6th/ 238, API 7th/ 306, 308; API 8th / 374, 375; CMDT 2003/ 243; 09/234*

***Bronchiectasis is not a premalignant condition.***

| **Complications of Bronchiectasis:** |
|---|
| • Massive hemoptysis. |
| • Empyema with or without bronchopleural fistula. |
| • Purulent pericarditis. |
| • Respiratory failure with chronic cor pulmonale. |
| • Metastatic abscesses in brain and bones. |
| • Secondary amyloidosis with nephrotic syndrome. |
| • Lung abscess: Bronchiectasis is a predisposing factor for Lung abscess API 7th/ 308. |

**61. Answer is A (HRCT) :** *Harrison 15th/206; Harrisons 16th/208; Harrison 17th/ 1630 Harrison 18th/p 2143*

*Presence of purulent sputum with recurrent haemoptysis suggests a diagnosis of* ***bronchiectasis****. HRCT is now the diagnostic procedure of choice having replaced bronchiography. – Harrison 16th/208*

**62. Answer is B (FEV1/FVC < 0.7):** *Harrison 18th/p 2154, 2155, 2156 Harrisons 17th/1587, 1588, 1638, 1639, 1640; Harrisons 16th/1499, 1500, 1550, 1551, 1501*

***Interstitial lung disease like interstial fibrosis are characterized by a normal or elevated $FEV_1$/FVC ratio which is characteristically > 0.7.***

**PFT results comparing obstructive and restrictive disease**
(may not be applicable for all forms of lung (disease)

| PFT Result | Obstructive Pattern | Restrictive Pattern |
|---|---|---|
| $FEV_1$ | ***Decreased (<80% predicted)*** *(Decreased out of proportion to FVC)* | *Decreased (May be preserved)* *(Decreased in proportion to FVC)* |
| FVC | *Decreased ( May be preserved)* | ***Decreased (<80% predicted)*** |
| $FEV_1$/FVC ($FEV_1$%) | ***Decreased (<0.7)*** | ***Normal or Increased (>0.7)*** |
| $FEF_{25-75}$ | *<50% predicted* | *Decreased in proportion to loss of lung volume* |
| TLC | *Normal or elevated* | *Decreased* |
| DLCO | *Normal* *Decreased in Emphysema* | *Decreased in intrinsic restrictive lung disease.* *Normal in neuromuscular or musculoskeletal restrictive disease* |

**$FEV_1$**=forced expiratory volume in one second; **FVC**=Forced Vital Capacity; **$FEF_{25-75}$**=Forced Expiratory Flow at 25%=75% vital capacity; **TLC**= Total Lung Capacity; **DLCO**=Diffusion Capacity of the Lung for Carbon monoxide.

**63. Answer is C (Decreased FEV1/FVC):** *Repeat : Refer previous question*

***Interstial lung diseases produce a restrictive pattern on Pulmonary function testing and are characterized by a normal or elevated $FEV_1$/FVC ratio which is greater than 0.7***
*$FEV_1$ and FVC are both reduced in interstitial lung disease but the decrease in FEV1 is in proportion to decrease in FVC and hence the FEV1/FVC ratio is normal (or increased)*

**64. Answer is B (Residual volume is increased):** *Harrison 18th/p 2160-2164 Harrison's 17th/1643-1646*

***Residual volume is decreased in patients with Interstitial Lung Disease***

**Progressive dyspnea and presence of bibasilar end-inspiratory crepitations suggests a diagnosis of interstitial lung disease**

*'Dyspnea is a common and prominent complaint in patients with Interstitial Lung Disease(ILD)' -Harrison 17th/1645*

*'Most commonly, physical examination reveals tachypnea and bibasilar end – inspiratory dry crackles which are common in most forms of ILD' – Harrison 17th/1645*

**Interstitial Lung Disease (ILD) may be associated with connective tissue diseases**
*'ILDs have been difficult to classify because > 200 known individual disease are characterized by diffuse parenchymal lung involvement either as primary condition or as a significant part of a multiorgan process, as may occur in connective tissue disorders (CTD's)'- Harrison 17th/1643*

**Interstial Lung disease produce a restrictive effect on Pulmonary Function Testing**
*'Most forms of ILD produce a restrictive defect with **reduced total lung capacity (↓TLC)**, functional residual capacity and **residual volume (↓RV).** Forced expiratory volume in one second (FEV1) and forced vital capacity (FVC) are reduced; but, the FEV1/FVC ratio is normal or increased' – Harrison 17th/1646*

**HRCT is a useful test for ILD**
*HRCT is the investigation of choice for Interstitial Lung Disease.*

**65. Answer is C (Usual Interstitial Pneumonia):** *Harrison 18th/p 2165 Harrisons 17th/1647; Robbins 8th/; Diffuse Lung Diseases (Springer) 1st (2006)/223; 'Imaging in Diffuse Lung Diseases' by Lynch & Lee (2000)/61*

***Presence of heterogenous, patchy fibrosis with fibroblastic foci is characteristic of Usual Interstitial Pneumonia***
*'The histologic hallmark and chief diagnostic criterion of **UIP** is a **heterogenous appearance**, interstitial inflammation, foci of proliferating fibroblasts **(fibroblastic foci)** dense collagen fibrosis and honey-comb changes. The interstitial **inflammation is usually patchy** and the histopathological changes affect the peripheral sub-pleural parenchyma most severely' – Harrisons 17th/1647*

*Usual Interstitial Pneumonia (UIP) is the histopathologic pattern of Idiopathic Pulmonary Fibrosis (IPF), a chronic fibrosing interstitial lung disease of unknown etiology (idiopathic)*

**Idiopathic Interstitial Lung Diseases / Idiopathic Interstitial Pneumonias**

- Idiopathic Interstitial Pneumonias are *interstitial lung diseases of unknown etiology* that *share similar clinical and radiological features* and are *distinguished primarily by the histopathological pattern on lung biopsy.*

| Histologic Name | Clinical Syndrome | Salient Pathological Features |
|---|---|---|
| ***Usual Interstitial Pneumonia (UIP)*** | *Idiopathic pulmonary fibrosis (Cryptogenic fibrosing alveolitis)* | *Temporally and spatially heterogeneous pattern with areas of normal lung, fibroblastic foci, and patchy sub-pleural fibrosis* |
| ***Desquamative Interstitial Pneumonia (DIP)*** | *Desquamative interstitial pneumonia* | *Homogenous intra-alveolar macrophage accumulation. Mild alveolar septal thickening* |
| ***Acute Interstitial Pneumonia (AIP)*** | *Acute interstitial pneumonia (Hamman-Rich syndrome)* | *Homogenous, diffuse lung injury with hyaline membranes, fibroblast proliferation* |
| ***Bronchiolitis Obliterans Organizing pneumonia (BOOP)*** | *Cryptogenic organizing pneumonia, (Idiopathic BOOP)* | *Multifocal organizing pneumonia, with granulation tissue and polyps in alveolar ducts and bronchioles* |
| ***Non-Specific Interstitial Pneumonia (NSIP)*** | *Nonspecific interstitial pneumonia* | *Temporally and spatially homogenous cellular inflammation with mild fibrosis* |
| ***Respiratory Bronchiolitis Associated Lung Disease(RBILD)*** | *Respiratory Bronchiolitis Associated Interstitial Lung Disease* | |

- Detailed Histopathological features are often required to distinguish various forms of Idiopathic Interstitial Pneumonias and hence these have been listed in a tabular form in the following table.

| Pathologic features of Idiopathic Interstitial Pneumonias | | | | | | | |
|---|---|---|---|---|---|---|---|
| ***Feature*** | ***AIP*** | ***BOOP*** | ***DIP*** | ***RBILD*** | ***UIP*** | ***NSIP-Cellular*** | ***NSIP-Fibrosing*** |
| Distribution | *Diffuse* | *Certrilobular* | *Diffuse* | *Mild, focal* | ***Patchy**, Sub-pleural* | *Diffuse* | *Diffuse/panacinar* |
| *Temporal appearance* | *Homogenous* | *Homogenous* | *Homogenous* | *Homogenous* | ***Herterogenous (Variegated)*** | *Homogenous* | *Homogenous* |
| *Septal Inflammation* | Scant | Scant | Scant | None | Scant, patchy | Prominent | Scant. diffuse |
| *Collagen fibrosis* | Absent | Scant | Variable Diffuse | Scant Patchy | ***Characterisitc Patchy*** | Absent | Diffuse |
| *Fibroblast proliferation* | *Diffuse (interstitial)* | *Diffuse (intralumiral)* | *Absent* | *Absent* | ***Fibroblastic Foci prominent*** | *Absent* | ***Fibroblastic Foci Rare*** |
| *Honey-combing* | Absent | Absent | Absent | Absent | Characteristic | Absent | Rare |
| *Alveolar macrophage* | Absent | Absent | Diffuse | Peribonchiolar | Occasional | Occasional | Occasional |
| *Hyaline membranes* | Occasional | Absent | Absent | Absent | Absent | Absent | Absent |

**66. Answer is B (HRCT):** *Grainger 4th/278, 279; Sutton 7th/33; Haga CT and MRI of the whole body 4th/838*

***High Resolution CT (HRCT) is investigation of choice for interstitial lung disease and bronchiectasis as it can delineate the lung parenchyma upto the level of secondary pulmonary lobule.***

**67. Answer is C (High Resolution CT):** *Grainger 4th/278, 279; Sutton 7th/33; Haga CT and MRI of the whole body 4th/838*

***High Resolution CT (HRCT) is investigation of choice for interstitial lung disease as it can delineate the lung parenchyma upto the level of secondary pulmonary lobule.***

**68. Answer is B (Thermoactinomyces Sacchari) :** *Harrsion 18th/2126,2117; Oxford American Handbook of Clinical Medicine 2nd/194*

***The classic presentation of farmer's lung results from inhalational exposure to Thermophilic Actinomycetes species.***
*Thermophilic actinomycetes species include Saccharopolyspora rectivirgula (formerly Micropolyspora faeni), Thermoactinomyces vulgaris, Thermoactinomyces viridis, and Thermoactinomyces sacchari*

**Farmer's lung** (Hypersensitivity pneumonitis, extrinsic allergic alveolitis)

- It is an immunologically mediated inflammatory disease of the lung involving the terminal airways.
- The classic presentation of farmer's lung results from inhalational exposure to Thermophilic *Actinomycetes* species. Thermophilic actinomycetes species include *Saccharopolyspora rectivirgula* (formerly *Micropolyspora faeni*), *Thermoactinomyces vulgaris, Thermoactinomyces viridis,* and *Thermoactinomyces sacchari,* among others.

*Farmer's Lung may occasionally result from exposure to various Aspergillus species also*

- Exposure to large quantities of contaminated moldy hay is the most common source of inhalational exposure for farmers who develop farmer's lung It is often a disease of dairy farmers who handle contaminated hay during the winter months. These organisms flourish in areas of high humidity and prefer temperatures of 40-60°C. Most cases of farmer's lung occur in cold, damp climates in late winter and early spring when farmers use stored hay to feed their livestock
- Patient typically presents 4-8 hours after exposure with fever, chills, malaise, cough, and dyspnea without wheezing

**Selected Examples of Hypersensitivity Pneumonitis (HP) with the Eponym 'Lung'**

| Disease | Antigen | Source of Antigen |
|---|---|---|
| Bird fancier's Lung<br>Breeder's, or Handler's lung | Parakeet, pigeon, chicken, turkey proteins | Avian droppings or feathers |
| Cheese washer's lung | *Penicillium casei* | Moldy cheese |
| Chemical worker's lung | Isocyanates | Polyurethane foam, varnishes, lacquer |
| Coffee worker's lung | Coffee bean dust | Coffee beans |
| Compost lung | *Aspergillus* | Compost |
| Farmer's lung | Thermophilic actinomycetes | "Moldy" hay, grain, silage |
| Furrier's lung | Animal fur dust | Animal pelts |
| Hot tub lung | *Cladosporium spp., Mycobacterium avium* complex | Mold on ceiling; contaminated water |
| Humidifier or air conditioner lung (ventilation pneumonitis) | *Aureobasidium pullulans, Candida albicans,* Thermophilic actinomycetes,[a]*mycobacterium* spp., other microorganisms | Contaminated water in humidification or forced-air air conditioning systems |
| Malt worker's lung | *Aspergillus fumigatus or A. clavatus* | Moldy barley |
| Metalworking fluid lung | *Mycobacterium spp., Pseudomonas spp.* | Contaminated metalworking fluid |
| Miller's lung | *Sitophilus granarius (wheat weevil)* | Infested wheat flour |
| Mushroom worker's lung | Thermophilic actinomycetes<br>*Hypsizygus marmoreus, Bunashimeji,* and other exotic mushrooms | Mushroom compost; mushrooms |
| Pituitary snuff taker's lung | Animal proteins | Heterologous pituitary snuff |
| Potato Riddler's lung | Thermophilic actinomycetes,[a]*Aspergillus* | "Moldy" hay around potatoes |
| Sauna taker's lung | *Aureobasidium* spp., other | Contaminated sauna water |
| Sausage worker's lung | *Penicillium nalgiovense* | Dry sausage mold |

**69. Answer is B (Thermoactinomyces Sacchari):** *Harrison 18th/2126, 2117; Oxford American Handbook of Clinical Medicine 2nd/194*

***Farmer's lung typically results from inhalational exposure to Thermophilic Actinomycetes.***

| *Thermophilic actinomycetes species include:* |
|---|
| *Saccharopolyspora rectivirgula (formerly Micropolyspora faeni)*<br>*Thermoactinomyces vulgaris,*<br>*Thermoactinomyces viridis,*<br>*Thermoactinomyces saccharri*<br>*Thermoactinomyces candidus* |

*Exposure to large quantities of contaminated 'Moldy' hay is the most common source of inhalational exposure for farmers who develop Farmer's lung*

**70. Answer is A (Byssinosis):** *Harrison 18th/ 2126, 2123; Park 21st/ 747*

***Byssinosis is a commonly seen Occupational Lung Disease in Textile Industry Workers (Cotton industry)***
*Byssinosis is an asthma-like condition caused by inhalation of cotton fiber dust over prolonged period of time. Workers occupationally exposed to cotton dust (but also to flax, hemp or jute dust) in the production of yarns for textile and rope making are at risk of Byssinosis. Exposure occurs throughout the manufacturing process but is most pronounced in the portions of the factory involved with the treatment of cotton before spinning (blowing, mixing, carding or straightening) Byssinosis is more common during milling and processing of cotton than during spinning.*

| *Offending Particles* | *Disease Name* | *Industry/ Agent* |
|---|---|---|
| ***Coal Dust*** | *Anthracosis* | *Mining* |
| ***Iron*** | *Siderosis* | *Mining* |
| ***Sugar Cane Fiber*** | *Bagassosis* | *Farming (Thermophilic Actinomycetes)* |
| ***Cotton Dust*** | *Byssinosis* | *Textile Industry* |
| ***Hay or Grain Dust*** | *Farmer's Lung (Hypersensitivity Pneumonitis)* | *Farming (Thermophilic Actinomycetes)* |

**71. Answer is D (Tobacco smoke):** *Harrison 17th/ 1643; Robbins Basis 6th/ 729t*

- Coal dust & Sulphur dioxide are mentioned as a cause Interstitial Lung Disease in the table.
- Thermophilic actinomycite is a well known cause
- ***So tobacco smoke is the answer of exclusion.***

**72. Answer is C (Rheumatoid Arthritis):** *Harrison's 18th/2739-2125*

***Caplan's syndrome refers to the association of Pneumoconiosis and Rheumatoid Arthritis.***

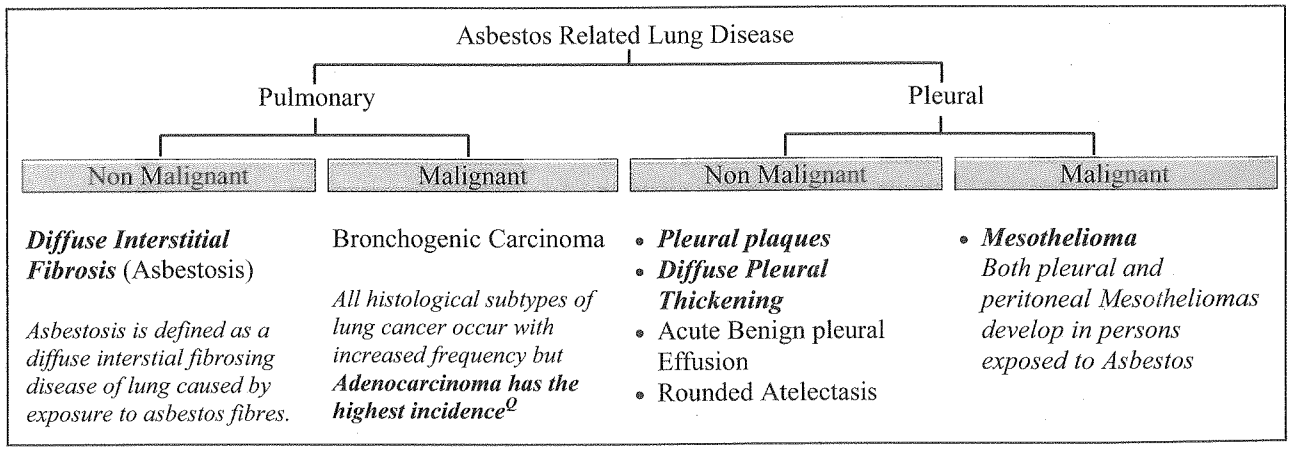
**Caplan's Syndrome** is a rare subset of pulmonary nodulosis characterized by the development of nodules and pneumoconiosis following *silica exposure* in patients with *Rheumatoid Arthritis*.

***Caplan's Syndrome*** first described in coal miners but subsequently found in patients with silicosis includes ***seropositive Rheumatoid arthritis with charachteristic pneumoconiotic nodules***. Silica has immunoadjuvant properties and is often present in anthractic coal dust.

***Felty's syndrome***$^{Q}$ *is defined by the clinical triad of Neutropenia, Splenomegaly and Nodular RA, typically seen in late stages of severe Rheumatoid Arthritis - Harrison's 18th/2740*

**73. Answer is C (Emphysema):** *Robbins 7th/736; Harrison 18th/p2161; Harrisons 17th/1612,1613; Fishman's pulmonary Diseases 4th/943*

***Emphysema has not been mentioned as a feature of Asbestos related lung disease.***



74. **Answer is E (All of the above) :** *Refer previous question*

***Asbestosis may be associated with Bronchogenic carcinoma, Mesotheliomas (pleural and peritoneal) and Pulmonary fibrosis.***

75. **Answer is A (Pleural plaques):** *Harrison 18th/p 2123, 2024; Harrisons 17th/1614*

***Pleural plaques are characteristically associated with Asbestosis and not silicosis***

**Silicosis has predilection for upper lobes**

*'Radiographs typically show fine nodularity in the upper zones of the lung' –Robbins 7th/735*
*'Rounded opacities appear in the upper lobes on chest radiograph' – Harrison 17th/1614*

**Silicosis is associated with calcific Hilar Adenopathy**
*Calcification of hilar lymph nodes may occur in as many as 20% of cases and produce a charachteristic "egg shell" pattern.*

**Silicosis is associated with Tuberculosis**
*'Because silica is cytotoxic to alveolar macrophages, patients with silicosis are at greater risk of acquiring lung infections that involve these cells as a primary defense including mycobacterium tuberculosis, atypical mycobacteria and fungi' – H17th/1614*

76. **Answer is C (Asbestosis and smoking act synergistically to cause lung cancer):** *Harrison 18th/ 2123-2125; Oxford Handbook of Respiratory Medicine 3rd/114*

***Asbestosis and smoking act synergistically to cause lung cancer.***

*'There is significant interactive effect of smoking and asbestos exposure that results in greater risk of Lung Cancer than what would be expected from the additive effect of each factor' - Harrison*

**Asbestosis and smoking act synergistically to cause lung cancer**

- Lung cancer is the most common cancer associated with asbestos exposure.
- Persons with more exposure are at greater risk of disease
- There is significant interactive effect of smoking and asbestos exposure that results in greater risk than what would be expected from the additive effect of each factor

**Pleural Plaques in Asbestosis may be asymptomatic and imply only prior exposure to Asbestos**

- Pleural Plaques are believed to be the most common manifestations suggesting Asbestos exposure
- They are characterized by thickening or calcification along the parietal pleura particularly along the lower lung fields, the diaphragm and the cardiac border.
- Without additional manifestations pleural plaques imply only exposure, not pulmonary impairment
- These are usually asymptomatic although if extensive, they may be associated with breathlessness

**Coal Workers Pneumoconiosis is not associated with Increased Risk of Lung Cancer**

- *CWP is not associated with an increased risk of Tuberculosis or Primary Lung cancer*

**Silicosis is associated with an increased risk of Tuberculosis**

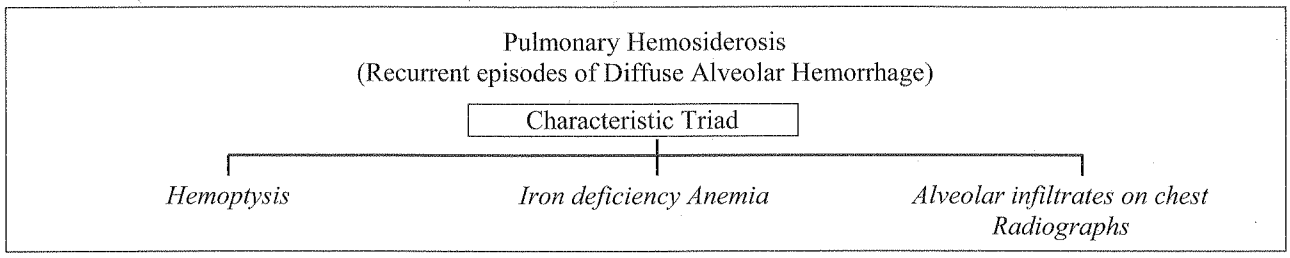
- *Silicosis is associated with an increased risk of Tuberculosis and Primary Lung Cancer*

77. **Answer is A (Eosinopenia):** *Nelson 18th/1824*

***Eosinopenia is not a feature of Idiopathic Pulmonary Hemosiderosis***

Idiopathic Pulmonary Hemosiderosis (IPH)
IPH is a disorder of unknown etiology characterized by recurrent episodes of Diffuse Alveolar Hemorrhage (DAH)

*It has been classically characterized by the triad of iron deficiency anemia, hemoptysis and alveolar infiltrates on chest radiographs.*




**78. Answer is B (Alveolar capillary constriction):** *Crofton and Douglas 5th/1333; Color Atlas & Text of Pulmonary Pathology 1st/265*

***Idiopathic Pulmonary Hemosiderosis is associated with alveolar capillary dilatation and not alveolar capillary constriction.***

Pathological Features of Idiopathic Pulmonary Hemosiderosis

- *Bland Alveolar hemorrhage (without capillaritis or inflammation of blood vessels)*
- *Hyperplasia of type II pneumocytes*
- *Alveolar capillary **dilatation** and tortuosity*
- *Hemosiderin laden macrophages in alveolar spaces of interstitium*

**79. Answer is D (Wegener's granulomatosis)** : *Harrison 18th/p 2119 Harrison 17th/1610*

*Pulmonary infiltrates with eosinophilia (PIE, eosinophilic pneumonias) include distinct individual syndromes characterized by eosinophilic pulmonary infiltrates and commonly, peripheral blood eosinophilia*
***ABPA, Loeffler's pneumonia, Churg Strauss Syndrome and Tropical pulmonary eosinophilia may all be associated with Eosinophillic Pulmonary Infiltrates (Pulmonary Eosinophilic Pneumonias)***

**Pulmonary Infiltrates with Eosinophilia (Pulmonary eosiniophilic pneumonia)**

| Etiology Known | Idiopathic |
|---|---|
| *Allergic bronchopulmonary mycoses* | *Loeffler's syndrome* |
| *Parastitic infestations* | *Acute eosinophilic pneumonia* |
| *Drug reactions* | *Chronic eosinophilic pneumonia* |
| *Eosinophilia-myalgia syndrome* | *Allergic granulomatosis of Churg and Strauss* |
| | *Hypereosinophilic syndrome* |

**80. Answer is D (Asbestosis):** *Imaging of Diffuse Lung Disease (PMPH-USA, 1999)/ 40; Examination Medicine (Elsevier Australia, 2009)/88, 89*

***Lower lobe fibrosis is seen in Asbestosis.***
*Silicosis, Sarcoidosis and Cystic Fibrosis are all associated with Upper Lobe Fibrosis*

| Upper Lobe Fibrosis | Lower Lobe Fibrosis |
|---|---|
| **Fibrotic Disease** | **Fibrotic Disease** |
| • *Old Granulomatous Infection (Tuberculosis; Histoplasmosis; Coccidioidomycosis)* | • *Idiopathic Pulmonary Fibrosis* |
| • *Sarcoidosis* | • *Asbestosis* |
| • *Silicosis, Berylliosis* | • *Collagen Vascular Disease (SLE; Systemic Sclerosis; RA)* |
| • *Coal Worker's Pneumoconiosis* | • *Drugs (Busulphan; Bleomycin; Methotrexate etc.)* |
| • *Ankylosing Spondylitis* | |
| • *Radiation Pneumonitis* | |
| • *Chronic Hypersensitivity Pneumonitis* | |
| **Airway Disease** | **Airway Disease** |
| • *Cystic Fibrosis* | • Chronic Aspiration |
| • *Allergic Bronchopulmonary Aspergillosis (ABPA)* | • Basal *Bronchiectasis* |

## Allergic Bronchopulmonary Aspergillosis (ABPA)

**81. Answer is D (Occurrence in patients with old cavitatory lesions):** *Harrison's 15th/ 1466; 16th/ 296; 17th / 1610 Harrison 18th/p 2120*

***Definitive major and minor diagnostic criteria have been defined for diagnosis of Allergic bronchopulmonary aspergillosis. Occurance in patients with old cavitatory lesion is not a part of either of these.***

***Allergic bronchopulmonary aspergillosis*** is a pulmonary hypersensitivity disorder caused by allergy to fungal antigens that colonize the tracheobronchial tree. It most commonly occurs in atopic asthmatic individuals in response to antigen of aspergillus species.

| Main diagnostic criteria | Secondary diagnostic criteria |
|---|---|
| 1. *Clinical history of Asthma* [Q] | 1. *History of brownish plugs in sputum* |
| 2. *Pulmonary infiltrates (transient / fleeting or fixed)* [Q] | 2. *Indentification / culture of A. fumigatus from sputum* |
| 3. *Peripheral eosinophilia (> 1000 /μL)* [Q] | 3. *Late skin reactivity to aspergillus antigen – CMDT* |
| 4. *Immediate skin reactivity to Aspergillus antigen (wheal and flare response)* | 4. *Elevated IgE (and IgG) class antibodies specific for A. fumigatus – Harrisons* |
| 5. *Serum precipitins to A. fumigatus* | |
| 6. *Elevated serum IgE levels* [Q] *(>1000ng/ml)* | |
| 7. *Central / proximal bronchiectasis* [Q] | |

Note

*Elevated IgE (and IgG) class antibodies specific for A. fumigatus has been mentioned as a secondary diagnostic criteria in Harrison's textbook while Fishman's textbook includes this as a main/major diagnostic criteria.*

**82. Answer is A (Peripheral eosinophilia (>0.1 × $10^9$/$mm^3$)):** *Fishman's Pulmonary Diseases and Disorders 4th/2299; Harrison 18th/p 2120 Harrison 17th/1610*

***Peripheral blood eosinophilia with eosinophil count >1000/$mm^3$ is included in the primary diagnostic criteria (and not an eosinophil count > 0.1 × $10^9$/$mm^3$)***

Criteria for the Diagnosis of ABPA Primary

| Primary |
|---|
| • *Episodic bronchial obstruction (asthma)* |
| • *Peripheral blood eosinophilia (>1000/$mm^3$)* |
| • *Elevated serum IgE concentrations (>1000ng/ml)* |
| • *Immediately type skin reactivity to Aspergillus antigens* |
| • *Precipitating serum antibodies (precipitants) against Aspergillus antigens* |
| • *Elevated serum IgE and/or IgG antibodies specific to A. fumigatus** |
| • *History of pulmonary infiltrates (transient/ fleeting or fixed) on chest radiographs or CT scans* |
| • *Central proximal bronchiectasis on chest CT* |
| **Secondary** |
| • *A. fumigatus in sputum (by repeated culture or microscopic examination)* |
| • *History of expectoration of brown plugs or flecks* |
| • *Arthus reactivity (late skin reactivity) to Aspergillus antigen* |

**Elevated IgE (and IgG) class antibodies specific for A. fumigatus has been mentioned as a secondary diagnostic criteria in Harrison's textbook while Fishman's textbook includes this as a main/major diagnostic criteria.*

**83. Answer is D (Bronchopulmonary Aspergillosis):** *Harrison 18th/2120; 17th/ 1610; CMDT 2002/ 296; 2008/222; 2009/234*

***Coexistence of repeated of bronchospasm (asthma), Central (perihilar) bronchiectasis and haemoptysis suggest a diagnosis of allergic bronchopulmonary aspergillosis.***

The questions gives us three leads: bronchospasm, hemoptysis, bronchiectasis.

- Presence of repeated episodes of bronchospasm indicates towards a possible existence of asthma.
- Hemoptysis, central bronchiectasis are well known complications of Allergic Broncho Pulmonary Aspergillosis.

*All three of these features are consistent with the diagnosis of ABPA.*

**84. Answer is B (Pleural effusion):** *Harrison's 16th/ 1188; 17th/ 1610; API 8th / 392 Harrison 18th/p 2119, 2120*

***Pleural effusion is not seen as part of allergic bronchopulmonary Aspergillosis***

- ABPA occurs in patients with preexisting ***asthma*** and cystic fibrosis. – Harrisons
- ABPA causes intermittent episodes of wheezing, pulmonary infiltrates, sputum and ***blood eosinophilia***, low grade fever and brownish or greenish flecks in the sputum.
- Patients with repeated exacerbations develop ***central bronchiectasis*** and progressive loss of pulmonary function.

**85. Answer is E (Lower lobe predominance):** *Fishman's Pulmonary diseases 4th/2296*

***ABPA predominant involves the upper lobes and not lower lobes***

**Upper Lobe Predominance**
*'ABPA Lesions are either focal or bilateral and tend to occur more frequently in Upper lobes' - Fishman's 4th/2296*

**Proximal (central) Branchiectasis is a charachteristic feature**
*'Presence of proximal (central) bronchiectasis which is charachterized by normal filling of bronchii distal to the saccular bronchial lesion is considered a hallmark for diagnosis of ABPA' - Fishman's 4th/2296*

**IgE > 1000 ng/ml, Eosinophils >1000/mm$^3$ and elevated IgG/IgM antibodies are all criteria for diagnosis of ABPA**

**86. Answer is B (It is highly contagious):** *Current Diagnosis and Treatment in Infectious Diseases (CIDT) 1st/751; Harrisons 17th/1257,1256 Harrison 18th/p 1655, 1656*

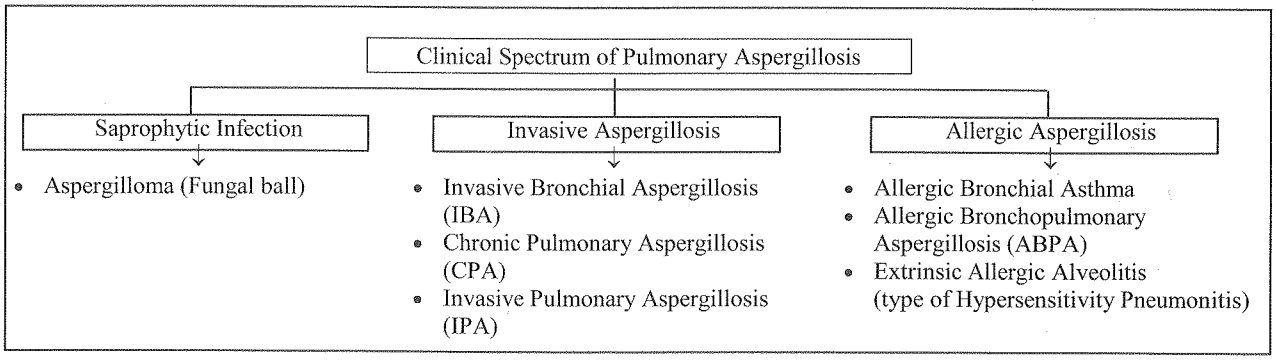
***Human Aspergillosis mostly results from inhalation of conidia and is not a contagious disease. Person to person transmission does not occur – Current diagnosis and Treatment in Infections Disease***

**Aspergillosis is not a contagious disease** (CIDT/751; Harrison 17th/1257)

- It is not a contagious disease and person to person transmission does not occur
- Routes of transmission include
  - Inhalation of conidia(major route)-Environmental Exposure
  - Direct inoculation into skin
  - Direct inoculation into blood amongst drug abusers
- Nosocomial infection may occur amongst hospitalized, immunocompromised patients

**Aspergillosis is common in preexisting tuberculosis and cystic disease**
*'Patient with chronic pulmonary aspergillosis have a wide spectrum of underlying pulmonary disease including tuberculosis and sarcoidosis' – Harrisons*
*'Preexisting cavitatory lesions predispose to the formation of Aspergilloma or fungal ball' (CIDT)*

**Aspergillus fumigatus is a known cause for bronchopulmonary Aspergillosis**




**Aspergillus niger more commonly colonizes the upper respiratory tract and causes otitis externa** *(Harrison)*

*The most common species of Aspergillosis causing pulmonary infections is Aspergillus Fumigatus.*
*The most common species of Aspergillosis causing otitis externa is Aspergillus niger.*

**87. Answer is C (Extrinsic Allergic Alveolitis) :** *Fishman's pulmonary diseases and disorders 4th/2295*

***Diffuse pulmonary infiltrates on X-Ray with normal levels of IgE and absence of peripheral eosinophilia is characteristic of Extrinsic Allergic Alveolitis.***

Hypersensitivity Reaction to Aspergillus

*Hypersensitivity Lung diseases that result from exposure to A. Fumigatus allergens include Bronchial Asthma, ABPA and Extrinsic Allergic Alveolitis (Hypersensitivity Pneumonitis)*

| In Atopic Individual | In Non atopic Individuals |
|---|---|
| *Allergic Bronchial Asthma and ABPA* | *Extrinsic Allergic Alveolitis (Hypersensitivity penumonitis)* |
| Allergic Bronchial Asthma and ABPA are seen in atopic individuals and immune response is IgE mediated | Extrinsic Allergic Alveolitis or Hypersensitivity penumonitis is seen in non atopic individuals and immune response is not IgE mediated. Immune response may involve cell mediated (type IV) or immune complex (Type III) reactions. |

| | Asthma | ABPA | Extrinsic allergic alveolitis |
|---|---|---|---|
| Pathology | Hypertrophied mucus glands | Colonization of airways, viscid mucoid impaction, tissue eosinophilia | Lymphocytic infiltration of interstitium, noncaseating granuloma |
| Radiological features<br>Early<br><br><br>Late | <br>Normal, hyperinflation<br><br><br>Normal, hyperinflation | <br>Migratory peripheral infiltrates, atelectasis, bronchiectasis<br>Fibrosis | <br>Diffuse alveolar-interstitial infiltrates<br><br>Reticulonodular interstitial opacities |
| Skin test reactions to Aspergilus antigens<br>Immediate<br>Delayed | <br>Positive<br>Negative | <br>Positive<br>Positive | <br>Positive<br>Positive |
| Peripheral eosinophilia | Negative | Positive | Negative |
| IgG Aspergillus precipitins | Positive (upt o 25%) | Positive | Positive |
| Serum IgE levels | Normal or mildly elevated | Marked deviation | Normal |

**88. Answer is B (Microfilaria in blood) :** *Harrison 16th/1263; 15th/1240; CMDT 2002/1520; 2009/1353-1354*

***In TPE, Microfilaria are rapidly cleared from the blood stream by the lungs. Thus, microfilariae are sequestrated in the lungs and are not found in the blood.***

**Tropical Pulmonary Eosinophilia**

*Tropical Pulmonary Eosinophilia (TPE) is a distinct syndrome that develops in individuals infected with Lymphatic filarial species.*

Clinical symptoms result from allergic and inflammatory reaction elicited by the cleared parasites.

**Features of Tropical Pulmonary eosinophilia (TPE) :**

- Male more commonly affected than females (4 : 1)
- History of resistance in filarial endemic region
- ***Paroxysmal cough and wheezing that are usually nocturnal*** Q
- Weight loss, low grade fever, adenopathy
- ***Eosinophilia > 3000 eosinophilia / μL*** Q
- ***Chest X-Ray : increased bronchovascular markings*** Q , *diffuse miliary lesions* Q , or ***mottled opacities***.
- *Restrictive changes on Pulmonary function test* Q
- *Elevated levels of IgE* Q & Antifilarial antibody titers.

***In TPE, Microfilaria are rapidly cleared from the blood stream by the lungs. Thus, microfilariae are sequestrated in the lungs and are not found in the blood.***

**89. Answer is A (Occult Filariasis) :** *Multiple references*

*Occult filariasis characterized by indirect evidence of filarial infection (antifilarial antibodies) is the cause of tropical pulmonary eosinophilia.*

*The term occult filariasis refers to a rare condition which is caused by hypersensitivity reaction to filarial antigens. The features of lymphatic filariasis are not present and microfilaria are not detectabe in the blood (but may be found in tissues). Indirect evidence of filarial infection is obtained by demonstrating antifilarial antibodies. Tropical Pulmonary Eosinophilia is considered to be such a variant of human filarial infection resulting from hypersensitivity reaction from destruction of microfilariae (liberated from Wuchereria Bancrofti and Brugia Malayi) in pulmonary capillaries.*

**90. Answer is C (Pulmonary eosinophilic granuloma) :** *CMDT 2002/ 296; 2005/ 243; API 8th / 391, 392, 393*

*All options mentioned in the question other than pulmonary eosinophilic granuloma are classified under this group of disorders termed 'pulmonary infiltrates with eosinophilia'.*

***Pulmonary infiltrates with eosinophilia:*** (PIE, eosinophilic pneumonias). Constituted by distinct individual syndromes characterized by eosinophilic pulmonary infiltrates and ***peripheral blood eosinophilia.***

These include:

| Etiology known | Idiopathic |
|---|---|
| • ***Allergic bronchopulmonary mycosis*** | • ***Loeffler's syndrome*** |
| • *Parasitic infestations* | • *Acute eosinophilic pneumonia* |
| • *Drug reactions* | • *Chronic eosinophilic pneumonia* |
| • *Eosinophilia myalgia syndrome* | • ***Allergic granulomatosis of Churg & Strauss Hypereosinophilic syndrome.*** |

**91. Answer is D>A (Wegener's granulomatosis > Allergic bronchopulmonary aspergillosis):** *Current Rheumatology Diagnosis and Treatment 2nd/276, 279; Bronchial Asthma 4th/350*

*The presence of fleeting opacities on serial skiagrams is consistant with a diagnosis of Allergic bronchopulmonary Aspergillosis and Wegner's granulomatosis. Associated Oligoarthritis however favours a diagnosis of Wegener's granulomatosis which is the single best answer of choice.*

**Oligoarticular Arthritis is a feature of Wegner's granulomatosis and is not mentioned as a feature of ABPA.**

*'Pauciarticular (oligoarticular) or Polyarticular arthritis may be seen in Wegner's granulomatosis'.*
*– Current Rheumatology 2nd/276, 279*

**Presence of fleeting opacities may be seen in ABPA and Wegner's granulomatosis**

| Fleeting opacities in ABPA | Fleeting opacities in Wegner's |
|---|---|
| 'Patients with ABPA typically have fleeting infiltrates on chest X-ray' – Crofton and Douglas Respiratory Diseases 5th/803 | 'Focal infiltrates which may be fleeting are seen' – Radiology of Chest Disease 3rd/103 |

| | ABPA | Wegner's |
|---|---|---|
| Age of Presentation | Most of the Age range is 20-40 years | Mean age at diagnosis is 50 years |
| Fever, weight loss Hemoptysis | May be seen | May be seen |
| Oligoarthritis | Not associated | Pauciarticular (oligoarticular), or Polyarticular arthritis may be seen |
| Fleeting opacities | May be seen | May be seen |

***The presence of Oligoarticular arthritis and age of presentation favour a diagnosis of Wegener's granulomatosis.***

Fleeting opacities are not associated with CA lung, and tuberculosis

## Pneumonias and Tuberculosis

### Bacterial Pneumonia

**92. Answer is A (Lobar Pneumonia):** *Fundamentals of Diagnostic Radiology 3rd/460; Textbook of Pulmonary Medicine by Behera 2nd/288*

***The most common pattern of Pneumonia seen in Klebsiella infection is Lobar Pneumonia***

*Streptococcus Pneumoniae (Pneumococcus) and Klebsiella are two common organisms that produce a lobar pattern of Pneumonia.*

**The radiographic pattern of pneumonia**

- **Lobar**
- **Lobular (bronchopneumonia)**
- **Interstitial**

| Lobar Pneumonia (Typical of Pneumococcal Pneumonia) | Lobular (Bronchopneumonia) (Typical of Staphylococcal Pneumonia) | Interstitial Pneumonia (Atypical Pneumonia) |
|---|---|---|
| • In lobar pattern of pneumonia organisms damage the terminal airspaces resulting in an outpouring of edema fluid in to the alveoli.<br>• Alveolar fluid becomes infected and spreads throughout a lobe by way of the pores of Kohn and the canals of lambert. Consolidation that results from this spread of infected fluid is confined within the pleural boundaries.<br>• Air bronchograms are seen within the opacification and are a characteristic feature of airspace disease.<br>• Pneumococcal pneumonia is the most common infection to produce lobar pattern. Klebsiella is also a common causative organism. | • In Lobular pattern the organism damages the terminal and respiratory bronchioles.<br>• Infection spreads along the intra-lobular airway until the pulmonary lobule is partially or totally involved.<br>• This process tends to be confined within the septal boundaries that surround the secondary pulmonary lobule.<br>• The resultant radiographic pattern is multiple, poorly defined, fluffy or patchy opacity that are scattered in the involved areas of the lung<br>• Many organisms produce this pattern including staphylococcus, Gram-negative pathogens and anaerobes. | • In Interstitial pattern organisms damage the bronchiolar walls and destroy mucosal cells.<br>• Airway walls become edematous and cellular infiltrates develop and spread to peri-bronchial tissues and interlobular septa.<br>• Linear, reticular, and small nodular opacities are typically seen with this process. Infiltrates may be reticular, reticular, reticulo-nodular or miliary.<br>• The usual agents producing this pattern of pneumonia are viruses and Mycoplasma. |

**93. Answer is B (Air Bronchogram Absent):** *Fundamentals of Diagnostic Radiology 3rd/460; Textbook of Pulmonary Medicine by Behera 2nd/288*

***Air Bronchogram sign is a characteristic feature of Pneumococcal Pneumonia.***

*Air Bronchogram is typically absent in Lobular Pneumonias (Bronchopneumonia) and Interstitial Pneumonias Pneumococcal Pneumonia is the most common pulmonary infection that produces lobar pattern of pneumonia. It is regarded as the typical prototype for Lobar Pneumonia. This type of Pneumonia is typically characterized by Homogenous (Non-Segmental) Consolidation involving an entire lobe. Because the airways are usually spared, air bronchograms (seen within the opacification) are common and characteristic. Cavitation is rare and Pleural effusion is uncommon.*

| Lobar Pneumonia (Typical of Pneumococcal Pneumonia) | Lobular (Bronchopneumonia) (Typical of Staphylococcal Pneumonia) | Interstitial Pneumonia (Typical of Viral / Mycoplasma Pneumonia) |
|---|---|---|
| Lobar pneumonia is typical of pneumococcal pulmonary infection. | Bronchopneumonia is most typical of staphylococcal pneumonia. | Interstitial pneumonia is most typical of viral, mycoplasma and pneumocystis infection |
| Consolidation is typically Homogenous and Non-Segmental | Consolidation is typically Segmental | Consolidation is not a typical feature since they tend to involve the airway walls and alveolar septa |
| Air Bronchogram is common<br>Because the airways are usually spared, air bronchograms are common and significant volume loss is unusual | Air Bronchograms are absent<br>Exudate within the bronchi accounts for the absence of air bronchograms in bronchopneumonia. | Air Bronchograms are absent |

***Note:***
*Bronchopneumonia is the most common cause of multifocal patchy airspace opacities,*
*Bronchopneumonia is the most common pattern of Pneumonia*

**94. Answer is A (Lower Lobe Involvement):** *Differential Diagnosis in Conventional Radiology (Thieme) 3rd/ 496; Aids to Radiological Differential Diagnosis (Elsevier Health Sciences, 2013)/68; Critical Care Radiology (Thieme, 2011)/Table 2.19*

***Pneumococcal pneumonias have predilection to involve the right lower lobe, whereas Klebsiella usually affects one of the upper lobes.***

| Features | Pneumococcal Pneumonia | Klebsiella Pneumonia |
|---|---|---|
| Consolidation Pattern | • Lobar Consolidation with positive air bronchogram sign | • Lobar Consolidation with positive air bronchogram sign |
| Lobe Predilection | • Predilection to involve Lower Lobe (Any lobe may be involved)<br>• Usually Unilobar (Usually do not expand involved lobe) | • Predilection to involve Upper Lobe (Any lobe may be involved)<br>• Often Multilobar (Tendency to expand involved lobe) |
| Abscess | • Abscess formation uncommon | • Abscess Formation common |
| Pleural Effusion | • Pleural Effusion uncommon | • Pleural Effusion common |
| Cavitation | • Cavitation is rare | • Cavitation is common |

**95. Answer is A (Klebsiella):** *Manual of Clinical Problems in Pulmonary Medicine 6th/155*

***Klebsiella Pneumonia is also known as Friedlander Pneumonia.***
*Klebsiella initially described in 1882 by Friedlander was also known as Friedlander's bacillus. Community acquired Pneumonia caused by Friedlander's bacillus (Klebsiella) was termed as Friedlander Pneumonia.*

**96. Answer is C (Stretptococcus pneumonia):** *Robbins 7th /748*

*'Streptococcus pneumonia or pneumococcus is the most common cause of community acquired acute pneumonia – Robbins 7th/748*
*Lobar pneumonia refers to an acute bacterial infection that results in consolidation of a large portion of a lobe or an entire lobe. Streptococcus pneumonia produces a picture of lobar pneumonia.*

**97. Answer is A (Streptococcal pneumonia):** *Duke Radiology Case Review: Imaging, Differential Diagnosis, and Discussion (Lippincott Williams & Wilkins) 2ND/ 427; Grainger & Allison's Diagnostic Radiology Essentials (Elsevier Health Sciences) 2013/ 38; CMDT 2014/ 270*

***Streptococcus Pneumoniae (pneumococcus) is the most common organism responsible for round pneumonia.***

*Round Pneumonia is a spherical pneumonia that is usually seen in children due to the lack of collateral air drift. Streptococcus Pneumoniae (pneumococcus) is the most common organism responsible for round pneumonia. Round pneumonias are important as they may simulate a tumor mass from which they must be differentiated.*

**98. Answer is A (Gram –ve bacilli):** *Harrison 16th/ 1539; 17th/ 1625-1628; Ananthnarayan 6th/ 588*

'Nosocomial pneumonias are common in immunocompromised patients and are characterized by colorization of the nasopharynx by *'Gram negative bacilli'* followed by trickling of upper airway secretions into lower airways, resulting in pneumonia' – *API 7th/ 304*
*'In a national survey in United States, 64% of all microorganisms isolated from the lungs of patients with nosocomial pneumonias were gram negative bacilli' – Harrison 16th/ 1539.*
**Remember: Changing trend:**
*S. aureus (gram positive cocci) is the most common cause of nosocomial pneumonia in the United States - Harrison 16th/1539*
*Thus while overall gram negative bacilli are the most common of cumulative agents for nosocomial pneumonias,* ***Staph aureus is the most common individual etiological agent.***

**99. Answer is D (Thalassemia):** *Harrisons 17th/866*

***Thalassemia has not been mentioned in the list of conditions that commonly predispose to pneumococcal infection Thalassemia is the single best answer of exclusion.***

Conditions that commonly predispose to pneumococcal infection:

**Increased risk of exposure**
- *Day care centres*
- *Military training camps*
- *Prisons*
- *Shelters for the homeless*

**Respiratory infection, inflammation**
- *Influenza, other viral respiratory infections*
- *Air pollution*
- *Allergies*
- *Cigarette smoking*
- *Chronic obstructive pulmonary disease*
- *Other cause of chronic pulmonary inflammation of obstruction*

**Anatomical disruption of meninges (dural tear)**

**Defective antibody formation**
- Common variable hypogammaglobulinemia
- Selective IgG subclass deficiency
- Multiple myeloma
- Chronic lymphocytic leukemia
- ***Lymphoma***

**Defective complement function**

**Defective bacterial clearance**
- *Congenital asplenia, hyposplenia*
- *Splenectomy*
- ***Sickle cell disease***

**Multifactorial conditions**
- ***Infancy and aging***
- *Chronic disease*
- *Prior hospitalization*
- *Alcoholism*
- *Malnutrition*
- *HIV infection*
- *Chronic lung disease*
- *Glucocorticoid treatment*
- *Cirrhosis of liver*
- *Renal insufficiency*
- *Diabetes mellitus*
- *Anemia*
- *Coronary artery disease*
- *Fatigue, stress, and/or exposure to cold*

**100. Answer is B (Staphylococcal pneumonia):** *Robbins 7th/ed 383, 385; Oxford Hand book of Medicine 6th/ed 174; Differential Diagnosis is conventional Radiology 3rd/ 574*

***Cavitatory lesions and /or Pneumatoceles are characteristic of staphylococcal pneumonias.***

*Primary Pulmonary tuberculosis does not usually present with cavitatory lesions. Cavitatory lesions are a feature of post-primary or secondary tuberculosis*

**Cavitation is characteristic of Staphylococcal Pneumonia**

Cavitation suggests aggressive bacterial infections by bacteria such as Staph.aureus (and gram negative bacilli)

Characteristic Feature of Stapylococcal Pneumonias
- *Cavitation$^{Q}$ (single or Multiple thick walled cavities) (may be Bilateral)*
- *Pneumatoceles$^{Q}$ (Thin walled cystic spaces that may contain air fluid levels)*
- *Pleural Effusion$^{Q}$ / Empyema$^{Q}$ with or without bronchopleural fistulas (Pyopneumothorax)*
- *Abscess formation$^{Q}$*

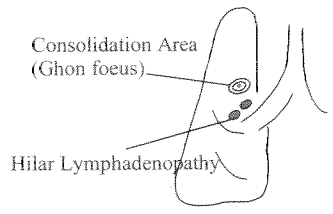
*Bacterial Pneumonas associated with cavitation: Review*
- *Staphylococcus$^{Q}$*
- *Kleibsella$^{Q}$*
- *Pseudomonas$^{Q}$*
- *Anaerobic bacteria*

**Cavitation is a feature of secondary / Post- primary Tuberculosis and not Primary Pulmonary Tuberculsis**

*The chorachteristic lesion in primary Tuberculosis is the fibrocasseous Ghon focus which presents as an area of consolidation on Radiographs*

***Cavitation is rare in primary tuberculosis (although it may be seen)***

*'Cavitation may be seen in primary tuberculosis but it is a rare feature' – Robbins*




**Tuberculous Primary Infection**

↓

Primary complex

**Consolidation**

(*Ghon focus*: Unilateral solitary *area of tuberculous consolidation* under the pleura in the lower part of upper lobe)

**Hilar Lymphadenopathy**

↓

Healing

Heals by ***fibrosis*** or calcification

**Interstitial lung diseases / Pneumoconiosis do not present with cavitatory lesions**

**101. Answer is A (Legionella):** *Harrison 18th/1237, 1238; 14th/ 930, 15th/ 945; 16th/ 872; 17th/ 930; Ananthnarayan / 377*

***Pneumonia in association with clinical clues in the form of high grade fever, confusion and diarrhea suggests a diagnosis of Legionnaire's pneumonia***

**Legionnaire's disease :**

- Legionnaires disease presents as an '***atypical pneumonia***'[Q] where a gram stained smear of sputum does not show organisms (Caused by *Legionella).*

| **Legionella** |
|---|
| • **Legionella** is a gram negative [Q], motile [Q], non-encapsulated bacilli [Q], classified under a miscellaneous group<br>• Man to Man transmission does not occur with Legionella. [Q]<br>• No animal reservoirs occur. [Q]<br>• Disease is limited to humans. [Q]<br>*Legionella survive and multiply inside free living amoeba and protozoa, distributed in natural reservoirs such as stagnant waters [Q], mud and hot spring.* |

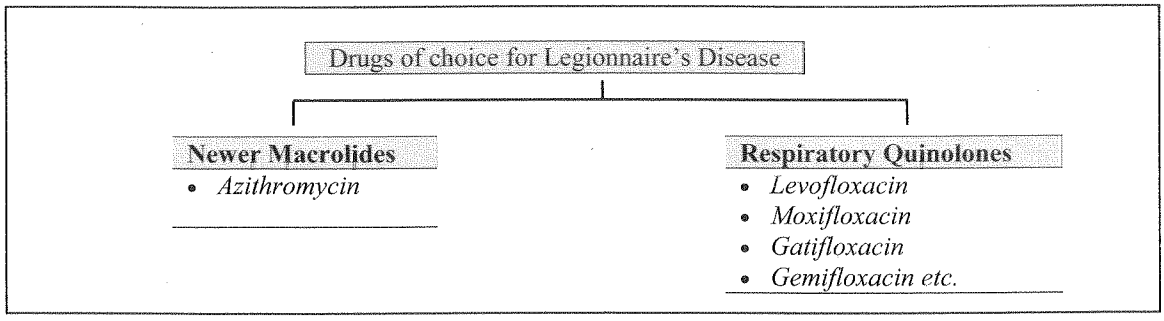
- Human infection is typically acquired by inhalation of aerosols, which form the only source of infection.[Q]
- Smoking and immunocompromised status are known risk factors.
- The disease occurs with unusual frequency among patients with hairy cell leukemia but not among patients with other types of leukemia

| **Common Risk factors for Legionnaires disease** |
|---|
| • Advancing age<br>• Immunocompromised patients:<br>- Transplant recipients, HIV, Glucocorticoid recipients<br>- Hairy cell leukaemia (monocyte deficiency and dysfunction)<br>• Chronic lung disease<br>• Smokers<br>• Diabetes mellitus (Javetz) |

- Presents as mild cough slightly productive sputum, sometimes streaked with blood, along with high fever and nonspecific symptoms such as malaise, fatigue, anorexia & headache.

| *Think about the diagnosis as Legionaire's disease whenever the question talks about a pneumonia like picture along with any of the these :* |
|---|
| a. Occurrence of illness in immunocompromised [Q], smokers [Q] or those with chronic lung disease [Q], or |
| b. Occurance of illness in an environment where potable water supply is known to be contaminated with Legionella |
| c. Onset of symptoms within 10 days of discharge from a hospital (I.P. 2 to 10 day), or |
| d. High fever, [Q] or |
| e. Gastrointestinal difficulties like diarrhea, [Q] or |
| f. Neurological abnormalities like confusion or altered Sensorium, [Q] or |
| g. Numerous neutrophils but no organisms revealed by gram staining of respiratory secretions, or |
| h. Hyponatremia [Q] is more common in Legionnaire's, than in any other form of pneumonia, or |
| i. Failure to respond to β-lactam drugs [Q] (penicillin or cephalosporins) and aminoglycosids antibiotics. |

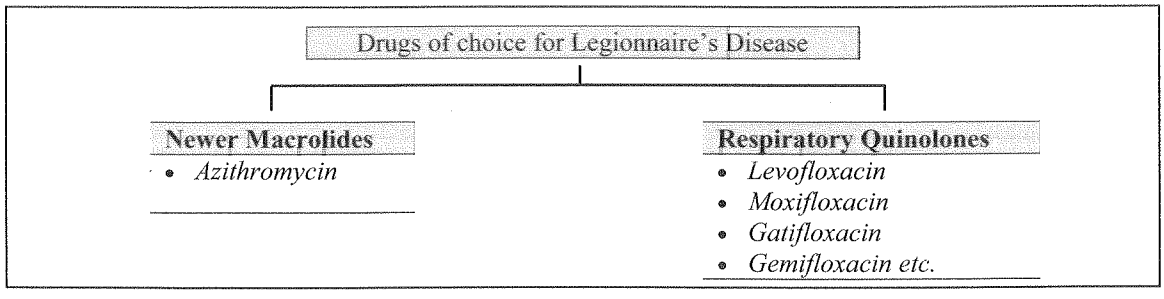
- Azithromycin and Respiratory Quinolones are the drugs of choice for Legionnaire's disease




**102. Answer is C (Azithromycin):** *Harrison 18th/p 1238, 1239, 1240 Harrison's 17th/930, 932*

***Azithromycin and Respiratory Quinolones are the drugs of choice for Legionnaire's disease***

*Development of pneumonia and diarrhea within 10 days after discharge from hospital hints to a possible diagnosis of Legionnaire's disease.* ***The drugs of choice for Legionnaire's disease include Azithromycin and Respiratory Fluoroquinolones such as Levofloxacin, Gatifloxacin, Gemifloxacin and Moxifloxacin.***




*Think about the diagnosis as Legionaire's disease whenever the question talks about a pneumonia like picture with onset of symptoms within 10 days of discharge from a hospital along with gastrointestinal difficulties like diarrhea (Refer previous question)*

**103. Answer is D (Levofloxacin):** *Harrison 17th /930, 932*

*Development of pneumonia and gastrointestinal symptoms (diarrhea & gripping abdominal pain) within 10 days after discharge from hospital hints to a possible diagnosis of Legionnaire's disease.* ***The drugs of choice for Legionnaire's disease include Azithromycin and Respiratory Fluoroquinolones such as Levofloxacin, Gatifloxacin, Gemifloxacin and Moxifloxacin.***

**104. Answer is B (Erythromycin is the drug of choice):** *Harrison 18th/p 1238, 1239 CMDT 2005/ 1373;2009/1278; Harrison 16th/ 871, 872; 17th / 929-932 Goodman Gillmons 10th/ 1154; Jawetz 23rd/ 313*

*'Azithromycin, Clarithromycin or a fluoroquinolone (eg Levofloxacin)* ***and not erythromycin*** *is the drug of choice for treatment legionellosis because of their excellent intracellular penetration and in vitro activity as well as desirable pharmacokinetic properties that permit oral administration and once or twice daily dosing - CMDT2005/1373; 09/1278*

| Agent | Disease | First choice | Second choice | Third choice |
|---|---|---|---|---|
| Legionella penumophilia | Legionnaire's disease | Azithromycin<br>Fluoroquinolone | Erythromycin | • Trimethoprim sulfomethoxazole<br>• Doxycycline |

**105. Answer is D (Any of the above):** *Harrison 18th/p 2136 Harrisons 16th/ 1536; 17th/1624, 1658, 1659; API 7th 308*

*Fever persisting even after treatment of pneumonia indicates treatment failure. All of the options mentioned should be considered when a patient with pneumonia fail to improve despite treatment.*

| Possibilities to consider when a patient with Community-Acquired Pneumonia fails to improve despite treatment |
|---|
| 1. Reconsider the diagnosis. Is this another illness presentinga pneumonia? Collagen vascular diseases involving the lung are frequently diagnosed at first as pneumonia. |
| 2. Are you treating the wrong pathogen? For example, if you are treating conventional bacterial causes of pneumonia, is this case actually due to Mycobacterium tuberculosis, Pneumocystis, or another **fungus**? |
| 3. Are you treating the right pathogen with the wrong drug? For example, if you are using nafcillin or claxacillin to treat Staphyloccos aureas and your patient is infected with methicillin resistant S. aureus you should be using vancomycin or linezolid. |
| 4. Is there a mechanical reason for the patient's failure to improve (e.g. obstructed bronchus due to **carcinoma** or seqestation of a segment of lung? |
| 5. Have you over looked an undrained or metastatic pyogenic focus(e.g.**empyema**, brain abscess, endocarditis, splenic, abscess, osteomyelitis? |
| 6. Does the patient have drug associated fever? |

**106. Answer is C (Bacterial pneumonia):** *API 7th/ 308; Harrisons 16th/ 1566; 17th/1658, 1659 Harrison 18th/p 2179*

*Empyema thoracic is collection of pus in pleural space and is synonymous with grossly purulent exudative parapneumonic effusions.*
***'In the pre antibiotic era aerobic bacteria (pneumococci and streptococci) were the most frequent causes but anaerobic bacteria are the most common causes now' – API***

## Atypical Pneumonia

**107. Answer is D (Kleibsella pneumonia) :** *Chandrasoma Taylor 3rd /516; Harrison 16th/882; 17th/ 1620 Harrison 18th/p2131*

***Kleibsella pneumonia presents as a typical 'air space' pneumonia with cough productive of purulent sputum.***
'Purulent sputum production and 'air space' diseases X Ray are typical' – *Harrison 16th/882*

| Causes of Atypical pneumonias |
|---|
| 1. Mycoplasma pneumonias |
| 2. Viral pneumonias - Influenza |
| - RSV |
| - Adenovirus |
| - Rhinovirus |
| - Rubeola |
| - Varicilla |
| - Corona virus |
| 3. Chlamydia pneumonia |
| 4. Coxiella burnetti |
| 5. Pneumocystis carinii |
| 6. Legionella |

**Corona virus is an infrequent cause of pneumonia.**
**SARS associated corona virus** *(SARS - CoV) caused epidemic of pneumonia from Nov 2002 to July 2003 - Harrison*

**108. Answer is B (Predominance of alveolar exudates) :** *Robbins 7th/751*

***Viral pneumonias are an example of 'atypical pneumonias' and are characterized by inflammatory reaction predominantly restricted within the walls of alveoli within the intertitium.*** *The alveoli may be free from exudates – Robbins.*
The alveolar septa are widened and edematous and usually have a mononuclear inflammatory infiltrate. *Alveoli may be free from exudates* but in many patients there is *accumulation of intraalveolar proteinaceous matrial*[Q], a cellular exudates and characteristically pink hyaline membranes. These changes reflect alveolar damage similar to that seen diffusely in ARDS.

| AIR Space Penumonia (Typical Pneumonia) | Interstitial Pneumonia (Atypical Pneumonia) |
|---|---|
| Exudate in alveoli i.e. consolidation | No exudate, alveoli are air filled i.e. no consolidation (infiltrate in interstitium) |
| Infiltrate is primarily of neutrophills (PMN) | Infiltrate is primarily lymphatic |
| Agents responsible are extracellular | Agents responsible are intracellular |
| Cough is productive of purulent sputum | Cough is dry |
| Chest X-ray shows alveolar pattern | Chest X-ray shows interstitial pattern |

**109. Answer is E (All of the above):** *Fishman's pulmonary diseases 4th/2362, Harrisons 17th/1267, 1268, 1269, Harrisons 11th/797 (old edition) Harrison 18th/p 1671, 1672, 1673*

***Pneumocytic carinii pneumonia is charachterized by a prominent eosinophilic exudate and mild interstitial pneumonitis. These is damage to type I pneumocytes and associated compensatory hypertrophy of type II pneumocytes.***

Classic Histopathology in Pneumocystis Pneumonia

| Intra- Alveolar Changes | Interstitial Changes |
|---|---|
| Prominent Eosinophilic foamy, vacuolated intraalveolar exudate (HE staining)<br>• Intra alveolar exudate contains the organisms, which can be identified in various stages of development (trophozoite and cystic stage) by the use of special stains such as<br>- Methamine silver / Toluidine stain<br>- Wright Giemsa stain<br>- Papanicolaou's stain<br>• Intraalveolar exudate also contains host serum proteins, debris, & surfactant proteins<br><br>Alveolar macrophages are present but not prominent in phagocytosis of organism.<br>• The principle host effector cells against pneumocystis are alveolar macrophages which ingest & kill the organism | Mild interstitial Pneumonitis<br>• Mononuclear interstitial cell infiltrate (mild)<br>• Damaged type I Pneumocytes<br>• Hypertrophy /proliferation of type II pneumocytis (Reparative response) *Pneumocystis attaches to, and damages type I pneumocytes. There is associated compensatory hypertrophy of type II pneumocytes.*<br><br>Note:<br>*Most compromised hosts display a mild mononuclear interstitial cell infiltrate however malnourished children display an intense interstitial plasma cell infiltrate which was responsible for the diseases early name of interstitial plasma cell pneumonia'* |

**110. Answer is B (Eosinophilic Alveolar Exudate):** *Fishman's Pulmonary Diseases 4th /2362, Harrisons 17th/1267, 1268, 1269 Harriosns 11th/ 797 (old edition)*; *Refer previous question Harrison 18th/p 1671, 1672, 1673*

***The most characteristic histopathological feature of pneumocystis carinii pneumonia in adults is predominantly alveolar, foamy vacuoloted, eosinophilic exudates.***

*Interstitial pneumonitis is usually mild and shows infiltration with PML and mononuclear cells.*

Note

| Pneumocystic Pneumonia in Adults | Pneumocystis Pneumonia in molnourished infants |
|---|---|
| ***In adults the disease appears to be predominantly alveolar***<br>*Air spaces (alveoli) are filled with a foamy, eosinophilic exudate and appear honey coombed*<br>*The intra-alveolar exudate consists of organisms, surface glycoprotein exudate and debri of macrophages and inflammatory cells.* | ***In infants the disease has a predominant interstitial component***<br>*The interstitium is filled with fluid plasma cells and lymphocytes.*<br>*These formed elements seem to overflow into air spaces which are filled with a frothy eosinophilic exudates.* |

**111. Answer is B (Pneumocystis carinii Pneumonia):** *Harrison 18th/ p1671,1672 Harrison's 17th/1267, 1268; Textbook of Pulmonary Medicines by Behera 2nd/ 413; Fishman's Pulmonary Diseases & Disorders 4th/ 1108, 2353, 2356, 2358*

***Presence of prolonged fever, weight loss and bilateral reticulonodular infiltrates in a person at increased risk of HIV (Long distance Truck drivers in India) suggests a diagnosis of Atypical pneumonia due to pneumocystis carinii infection.***

*Pneumocystic pneumonia is one of the most common AIDS – defining opportunistic infections and should be considered in any patient presenting with atypical pneumonia who is at increased risk of acquiring HIV (eg Professional sex workers, Homosexuals men, Intravenous drug users and Long distance Truck drivers in India)*

**Presentation of patient is consistant with diagnosis of Pneumocystic Pneumonia**

- Pneumocystis carinii is an important cause of Atypical Pneumonia in immunocompromised states especially AIDS
- Pneumocystic Pneumonia is recognized as one of the most common AIDS defining oppostunistic infections.

*'A diagnosis of Pneumocystic pneumonia should be considered in any patient presenting with sings / symptoms of Atypical Pneumonia in a patient who is at increased risk of acquiring HIV infection'*

| Long Distance Truck Drivers in India are considered a high risk population for contracting the HIV virus *(Nag, 1996)* |
|---|

- Charachteristic clinical manifestations include significant weight loss, fever, non productive cough and dysponea

| Clinical Manifestations *(Textbook of Pulmonary Medicine' by Behera 2nd/413)* |
|---|
| • *Profound **weight loss** (~ 100%)* |
| • ***Fever** (~ 97%)* |
| • *Dyspnea (~ 63%)* |
| • ***Non Productive cough** (~ 75%)* |

- The most charachteristic finding an chest X-Ray is bilateral diffuse infiltrates beginning in the perihilar region although various atypical manifestations including nodular lesions, cavitatory lesions etc have also been reported

| ***The classic finding on chest radiography consists of bilateral diffuse infiltrates beginning in the perihilar region*** |
|---|

*However no radiographic pattern is pathognomic for pneumocystic pneumonia.*

**Tuberculosis is *unlikely*** *as it usually present with productive cough* and the patient in question has a non productive dry cough. Also, *bilateral diffuse reticulonodular infiltrates are not charachteristic of Tuberculosis.*

**Interstitial Lung Diseases is *unlikely*** *as these disorders usually do not present with fever and weight loss*, although bilateral reticulonodular infiltrates may be seen on chest x-Ray.

*'With most interstitial lung diseases, constitutional symptoms like fevers, chills and weight loss are absent'*

*– Fishman's Pulmonary Diseases 4th/1108*

| **Note:** Patients with Acute Interstitial Pneumonias (Type of ILD) may present with the a similar clinical and radiological picture, but these disorders constitute only a small fraction of Interstitial Lung Diseases (< 1%). |
|---|

**Pneumococcal Pneumonia** *is unlikely as it presents with typical features of pneumonia including productive cough and consolidation on chest x-rays.* The patient in question has a form of *atypical pneumonia.*

| AIR Space Penumonia (Typical Pneumonia) | Interstitial Pneumonia (Atypical Pneumonia) |
|---|---|
| Exudate in alveoli i.e. ***consolidation*** | No exudate, alveoli are air filled i.e. ***no consolidation*** (infiltrate in interstitium) |
| Infiltrate is primarily of neutrophills (PMN) | Infiltrate is primarily lymphatic |
| Agents responsible are extracellular | Agents responsible are intracellular |
| ***Cough is productive of purulent sputum*** | ***Cough is dry*** |
| Chest X-ray shows alveolar pattern | Chest X-ray shows interstitial pattern |

**112. Answer is A (Usually associated with CMV infection):** *Washington manual of Pulmonary Medicine (2006)/ 104 Harriosns 16th/ 1194, 1195; Jawetz 24th/ 648, 649; 'Pneumocystic Pneumonia' by Wolzer & Cushion 3rd/418; CT scan of the body by Mathias /362*

**Pneumocystis Jiroveci may be associated with CMV infection but it is not usually associated with CMV infection.**

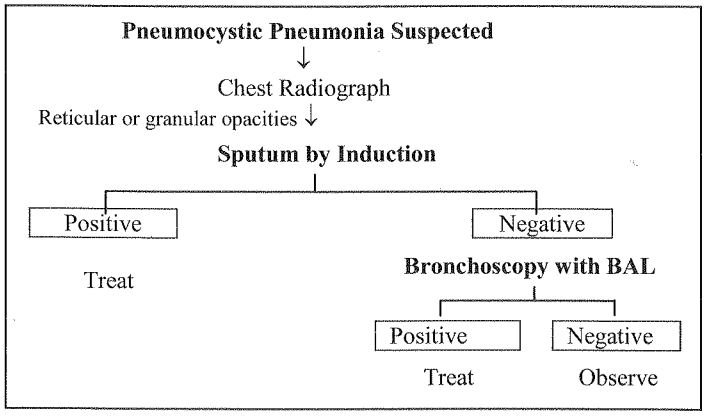
| *Pneumocystis Jiroveci is the new nomenclature for human infection with Pneumocystic carini (which is now used for organisms found in rats)* |
|---|
| Pneumocystis infection in Humans : P. Jiroveci |
| Pneumocystis infection in Rats : P. Carini |

- ***Pneumocystic Jiroveci disease and immunosupression***
  **'Pneumocystis Jiroveci does not cause disease in the absence of immuno supression'** – Jawetz 24th/648

  ***Note***
  *Pneumocystic Jiroveci may infect immunocompetent hosts but the disease (pneumocystis pneumonia) occurs only when the host is immunosupressed*
  Most individuals are infected in early childhood But pneumonia occurs in immunocompromised patients only either due to reactivation or new infection.

  *Persons at risk for Pneumocystic disease (Pneumocystosis)*
  - Acquired *Immunodeficiency* Disease (eg AIDS)
  - Patients Recieving *Immunosupressive* therapy (especially Glucocorticoids) for cancer, organ transplantation etc.
  - Children with primary *immunodeficiency* diseases
  - Premature malnourished infants (*immunodeficient*)

- ***Pneumocystic Pneumonia : Diagnosis***
  Diagnosis of Pneumocystic Pneumonia is based on specific identification of organism in respiratory specimen with appropriate histological staining
  - *Pneumocystis infection is usually diagnosed by sputum examination*
    *Sputum samples should always be obtained by induction (with hypertonic saline)*
    *Routine sputum specimen is often inadequate (Washington manual of Pulmonary medicine)*
  - *BAL forms the mainstay of diagnosis for Pneumocystic Pneumonia*
    *If organisms are not seen on induced sputum examination a Bronchoalveolar lavage specimen should be obtained. BAL forms the mainstay of diagnosis for Pneumocystic Pneumonia - Harrisons 16th*




- ***Pneumocystic Pneumonia and CMV infection*** ('Pneumocystic Pneumonia' by Wolzer & Cushion 3rd/418)
  *'Several studies have indicated that CMV is a risk factor for Pneumocystis Pneumonia in Renal transplant patients*
  These is however no convincing evidence to show a direct effect of the CMV virion on Pneumocystis'

  Thus we conclude
  Pneumocystic ***may be associated*** with CMV infection but in a few selected cases and special circumstances like Renal tansplantation. CMV is ***not usually associated*** with pneumocystic pneumonia.

- ***Pneumocystis Pneumonia and Pneumatocele***

  Pneumocystic Pneumonia ***may be associated*** with pneumotocele formation but Pneumatoceles are ***not associated in all cases*** of Pneumocystic pneumonia

  Pneumatocele: Differential Diagnosis *(CT scan of the body by Mathias /362)*
  - *Post infectious (Staphylococcal*$^{Q}$ and other bacterial infections)
  - ***Pneumocystic***$^{Q}$
  - Post traumatic (Laceration )
  - After treatment of metastasis (rare)

**113. Answer is B (Usually diagnosed by Sputum examination) :** Refer previous question

*Pneumocystis Jiroveci is usually diagnosed by sputum examination. This is the single best answer of choice amongst the options provided.*

- **Pneumocystic infection is usually diagnosed by sputum examination although mainstay of diagnosis for pneumocystic infection is Bronchoscopy with BAL**

  Sputum examination is the initial procedure of choice to confirm the presence of Pneumocystic Jiroveci infection

  ***P. Jiroveci infection is usually diagnosed by histopathological staining of an induced sputum specimen***
  BUT ⇓ BUT
  *Sputum examination is not the mainstay of diagnosis of P. Jiroveci infection.*
  Fibreoptic *Bronchoscopy with BAL which is more sensitive than sputum examination remains the mainstay of Pneumocystis diagnosis – Harrison 17th/1195*

- **Pneumocystis infection may occur in healthy individuals but disease due to Pneumocystic infection does not occur in the absence of Immunosupression**

  *'Serological endence suggests that most individuals are infected in early childhood' – Jawetz 24th/648*
  *'Most healthy children have been exposed to the organism by 3 to 4 years of age' – Harrisons 16th/1194*
  BUT ⇓ BUT
  *'In the absence of immunosupression P. Jiroveci does not casue disease' – Jawetz 24th/ 648*

- **Pneumocystic Jiroveci infection may be associated with CMV infection and may present with Pneumatocele (Not always)** (Refer previous question)

**Remember : Facts: Confusing statements**

- *Pneumocystis infection is usually diagnosed by sputum examination.* : *True*
- *Pneumocystis infection is usually diagnosed by routine sputum examination* : *False*
  *Routine sputum specimen are often inadequate. Sputum samples should be obtained by induction with hypertonic saline - Washington Manual*
- *Sputum examination is the mainstay of diagnosis for Pneumocystis* : *False*
  *Bronchoscopy with BAL is the mainstay of diagnosis – Harrison*
- *Pneumocystis infects only the immunocompromised host* : *False*
  *Most healthy individuals are infected with pneumocystis in early childhood – Jawetz*
- *Pneumocystic pneumonia occurs only in the immunocompromised host* : *True*
  *P. Jiroveci does not cause disease in the absence of immunsupression – Jawetz*

**114. Answer is A and D ($CD_4$ count <200 ml and oral condidiasis):** *Harrisons 17th/1269 Harrison 18th/p 1672, 1673*

*$CD_4$ count <200 and Oropharyngeal candidiasis are indications for prophylaxis against pneumocystis carini pneumonia.*

Indications for prophylaxis against Pneumocystic carinii

- An absolute $CD_4$ count <200/μL ($CD_4$ percentage <20%) (Primary prophylaxis)
- Oropharyngeal candidiasis (Primary prophylaxis)
- *Prior Pneumocystic carinii pneumonia (Secondary prophylaxis)*

Remember

Criteria for discontinuing primary prophylaxis

*$CD_4$ + Tcell count > 200 for ≥ 3 months*

**The drug of choice for primary and secondary prophylaxis is TMP- SMX**

**115. Answer is D (Fluoroquinolones):** *Harrison 15th/ 1184; 17th/ 1268, 1269; Goodman Gillman's pharmacology 10th/ 1156. Harrison 18th/p 1672, 1673*

***Fluoroquinolones are not used in the treatment of P. carinii infection.***

**Drugs used for treatment of *Pneumocystis carinii* infection include:**

| Agent | Disease | First choice drug | Second choice | Third choice |
|---|---|---|---|---|
| Pneumocystis carinii | Mild to moderate pneumonia | Trimethoprim Sulfamethoxazole | Trimethoprim – Dapsone<br>Clindamycin – Primaquine | Atovaquone |
| | Sever pneumonia | Trimethoprim Sulfamethoxazole | Pentamidene<br>Clindamycin-Primaquine | Trimetroxate |

**Drug of choice for all forms of pneumocystosis:** *Trimethoprim-Sulfamethoxazole (Cotrimoxazole)*

**116. Answer is B (Cotrimoxazole):** *Harrison 18th/ 1672, 1673*

***Trimethoprim/sulfamethoxazole or Cotrimoxazole is the drug of choice for all forms of Pneumocystis Pneumonias.***

*'Trimethoprim-Sulfamethoxazole which acts by inhibiting folic acid synthesis is considered the drug of choice for all forms of Pneumocystis Pneumonias. Therapy is continued for 14 days in Non-HIV-Infected patients and for 21 days in HIV-Infected patients' – Harrison 18th/1672*

**117. Answer is D (Erythromycin):** *Harrison 18th/p 1419 Harrison 16th/ 1010; 17th/ 1068, 1069;KDT 5th/ 688; CMDT 2009/238(t 9-9);2005/246*

***Erythromycin is used as a first choice drug for atypical pneumonia caused by mycoplasma pneumoniae-KDT***

*According to CMDT:*

| Agent / organism | Preferred: | Alternative: Antimicrobial therapy |
|---|---|---|
| Mycoplasma pneumoniae | Erythromycin or Doxycycline | Clarithromycin; Azithromycin, Fluoroquinolone |

**118. Answer is C (Cefotaxime is the drug of choice):** *CMDT- 2008/1125; 2009/238(t 9-9)*

***The drugs of choice for mycoplasma are Erythromycin and Doxycycline and not Cefotaxime.***

| Etiologic Agent | Drugs of First choice | Alternative Drugs |
|---|---|---|
| *Mycoplasmas* | *Erythromycin or Doxycycline* | *Clarithromycin,*<br>*Azithromycine*<br>*Fluoroquinolones* |

**119. Answer is A (Erythromycin):** *Harrison 18th/p 1430 Harrison 17th /1078; CMDT 2005/ 246; 2009/238(t 9-9)*

***Erythromycin is the answer of choice here as Doxycycline has been not provided in the options.***

**Drugs used for treatment of Chlamydia pneumonia :**

**According to CMDT:**

| Preferred agent | Alternative agent |
|---|---|
| Doxycycline | Erythromycin<br>Clarithromycin<br>Azithromycin<br>Fluoroquinolone |

**According to Goodman & Gillman's :**

| First choice drug | Second choice drug |
|---|---|
| Doxycycline<br>Azithromycin or<br>Clarithromycin or<br>Erythromycin | Fluoroquinolone |

**120. Answer is B (Tachyapnea):** *Harrison 16th/ 1538; Clinical/Anesthesiology 3rd/ 250*

***Aspiration pneumonitis** is characterized by an acute onset of dyspnea, tachypnea, bronchospasm and cyanosis with a chest radiograph often showing diffuse opacities. – Harrisons*

***Dyspnea & tachypnea are certainly the earliest manifestations to appear following aspiration of any material. The commonest and the earliest 'sign' of aspiration pneumonitis thus would be tachypnea.***

## Tuberculosis

**121. Answer is B (Unilateral hilar lymphadenopathy):** *Harrison 15th/ 1027*

***Unilateral hilar lymphadenopathy as part of the primary complex is a characteristic feature of primary tuberculosis***

**Primary tuberculosis:**

- It is the first infection with tubercle bacilli in individuals who have not been previously exposed to the organisms
- Seen in children Q
- Primary complex is characteristic

| Primary (Ghon) complex |
|---|
| • Unilateral enlarged hilar lymph nodes Q<br>• Ghon focus Q: Epitheloid-cell granulomatous inflammation (consolidation) at site of parenchymal infection. Usually small and subpleural most commonly located under pleura in lower part of upper lobe |

- Usually a symptomatic Q or manifested by a mild flu like illness at time of tuberculin conversion
- Lesion heal by fibrosis Q and may calcify Q
- Radiological evidence of healed primary infection may or may not be present Q

| Effects of primary tuberculosis |
|---|
| • Tuberculin positivity Q<br>• Partial immunity to tuberculosis Q: individual requires a higher dose to be reinfected by tubercle bacilli<br>• Presence of dormant tubercle bacilli |

**122. Answer is A (Cavitatory lesion):** *Harrisons 17th/1008-1011, Robbins 7th/383-385*

***Cavitatory lesions are a feature of post primary or secondary tuberculosis and not primary tuberculosis cases***
***Cavitation is rare in primary tuberculosis***
**Cavitation is a feature of secondary Tuberculosis (Robbins)**

*Cavitation occurs readily in the secondary form.*
*Indeed cavitation is almost inevitable in neglected secondary tuberculosis.*
***Cavitation may be seen in primary tuberculosis but it is a rare feature.*** *- Robbins*

**Fibrocasseous lesion are charachteristic in primary Tuberculosis**
*The charachteristic pulmonary lesion in primary tuberculosis is a Ghon's focus, which is in fact a fibrocasseous lesion showing marked granulomatous inflammatory reaction with casseous necrosis.*

**Phlectenular conjunctivitis is a feature of primary tuberculosis**
***Phlyctenular conjunctivits is a hypersensitivity reaction in the eye to the presence of TB bacilli elsewhere in the body. It is commonly seen in children with primary tuberculosis***

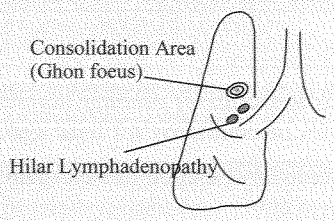
The onset of tubercular infection may be accompanied by erythema nodosum or phlyctenular conjunctivitis which are regarded as hypersensitivity reactions to mycobacteria. These lesions reflect tuberculin conversion in primary tuberculosis

| Hallmarks indicating Hypersensitivity to Mycobacteria in Primary pulmonary TB |
|---|
| • *Erythema nodosum*<br>• *Phlyctenular conjunctivitis* |

**Pleural effusion is common in primary tuberculosis**
*'Pleural effusion is found in upto 2/3 of cases of primary tuberculosis and results from penetration of bacilli into the pleural space from an adjacent subpleural focus' - Harrison*

**123. Answer is None (All may be seen ):** *Harrison 18th/1343-1346;17th/1008-11, Robbins 7th/383-85;API Medicine 7th/ 310*

*All features mentioned may be seen in the normal course of a primary tuberculous infection.*




**Tuberculous Primary Infection**
↓
Primary complex
**Consolidation**
(*Ghon focus*: Unilateral solitary *area of tuberculous consolidation* under the pleura in the lower part of upper lobe)
**Hilar Lymphadenopathy**
↓
Healing
Heals by ***fibrosis*** or calcification

**Pleural effusion may be seen in primary tuberculosis**

*'Pleural effusion is found in upto 2/3 of cases of primary tuberculosis and results from penetration of bacilli into the pleural space from an adjacent subpleural focus' – Harrison*

**124. Answer is A (Lungs):** *Robbins 8th/chap 8; Oski's Pediatrics 4th/1144, Principles of Pulmonary Medicine (Elsevier) 5th/307*

***The most common primary site for primary tuberculosis is the Lung.***

*'Primary site is the Lung in upto 95% of cases' - Oski's Pediatrics*

*'For both primary and reactivation tuberculosis the lungs are the most commonly affected site.'*

*- Principles of Pulmonary Medicine (Elsevier) 5th/107*

| |
|---|
| *Most common primary site for Primary Tuberculosis is Lungs*[Q] |
| *Most common site for Post-Primary Reactivation Tuberculosis is Lung*[Q] |
| *Most common primary site for congenital tuberculosis is Liver*[Q] |
| *Most common site /organ involved in congenital tuberculosis in Lung*[Q] |

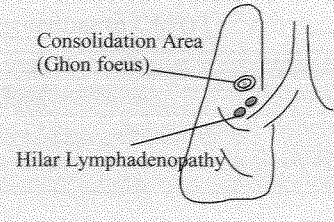
**Primary tuberculosis:**

- It is the first infection with tubercle bacilli in individuals who have not been previously exposed to the organisms
- Seen in children [Q]
- Primary complex is characteristic

**Primary (Ghon) complex**
- Unilateral enlarged hilar lymph nodes [Q]
- Ghon focus [Q]: Epitheloid-cell granulomatous inflammation (consolidation) at site of parenchymal infection. Usually small and subpleural most commonly located under pleura in lower part of upper lobe

- Usually a symptomatic [Q] or manifested by a mild flu like illness at time of tuberculin conversion
- Lesion heal by fibrosis [Q] and may calcify [Q]
- Radiological evidence of healed primary infection may or may not be present [Q]

**Effects of primary tuberculosis**
- Tuberculin positivity [Q]
- Partial immunity to tuberculosis[Q]: individual requires a higher dose to be reinfected by tubercle bacilli
- Presence of dormant tubercle bacilli




**Tuberculous Primary Infection**
↓
Primary complex
**Consolidation**
(*Ghon focus*: Unilateral solitary *area of tuberculous consolidation* under the pleura in the lower part of upper lobe)
**Hilar Lymphadenopathy**
↓
Healing
Heals by ***fibrosis*** or calcification

**125. Answer is B (Liver):** *'Avery's Diseases of the Newborn' (Elseiver 2005)8th/544; Essentias of Tuberculosis in Children by Seth & Kabro (Jaypee) 2006/299,300*

***Primary Complex in the Liver suggests congenital tuberculosis.***

*'The only lesion in a neonate that is unquestionably associated with congenital infection is a primary complex in the liver; all others may be acquired congenitally or postnatally'- Avery's Diseases of the New born*

**Diagnostic Criteria for Congenital Tuberculosis**

| Beitzke' Criteria (1935) | Revised Criteria by Cantwell (1994) |
|---|---|
| i. Bacteriological Proof of Tuberculosis<br>***ii. Primary complex in Liver***<br>iii. If primary complex is lacking in Liver then tuberculosis can be considered congenital only if:<br>a. Tuberculous lesions present in fetus or newborn are only few days old<br>b. Or in an older infant extrauterine infection can be excluded with certainity | i. Lesion in first week of life<br>***ii. A primary hepatic complex or caseating hepatic granuloma***<br>iii. Tuberculous infection of placenta or maternal genital tract<br>iv. Exclusion of possibility of postnatal transmission by a thorough investigation of contacts including the infant's hospital attendants or birth attendants |

**126. Ans. Answer is B (Liver):** *Thurlbeck's Pathology of the Lung (Thieme)2005/223; Avery's Diseases of the Newborn/ (Lippincott)8th/543, 543, 544, 545; Oski's Pediatrics 4/h/1151; Liver Disease in Children (Cambridge University Press 2007/876)*

***The most common primary site for, true congenital tuberculosis (primary complex in congenital tuberculosis) is Liver (followed by Lungs).***

**Congenital Tuberculosis**

| Congenital Tuberculosis caused by ***Transplacental spread*** (Hematogenous) | Congenital Tuberculosis caused by ***aspiration of infected amniotic fluid*** | Congenital Tuberculosis caused by ***ingestion of infected amniotic fluid*** |
|---|---|---|
| *Most common Primary site of infection is Liver (Hematogenous infection leads to miliary disease)* | *Most common Primary site of infection is Lungs* | *Most common Primary site of infection is Gastrointestinal Tract* |
| *Since Lungs are eventually involved in most cases of congenital tuberculosis where Liver is the primary site of infection, Lungs are the most commonly involved sites in Congenital Tuberculosis* | | |

**Congenital Tuberculosis**

- True congenital Tuberculosis is defined as tuberculosis occurring in infants as a result of infection with M. Tuberculosis during intrauterine life.
- Three modes of fetal infection have been proposed
  a. Transplacental (Hematogenous infection via the umbilical vein)
  b. Fetal aspiration of infected amniotic fluid
  c. Fetal ingestion of infected amniotic fluid
- When infection enters the fetus through the umbilical veins, the primary tubercular lesions (primary complex) develops in the liver. (Lesions may also develop in the lungs suggesting further passage of bacilli through the ductus venosus)

  *'The only lesion in the neonate that is unquestionably associated with congenital infection is a primary complex in the liver; all others may be acquired congenitally or postnatally*
- When infection enters the fetus through the aspiration / inhalation of infected amniotic fluid the primary lesions (primary complex) develops in the lungs.

  *Tuberculous involvement of Lungs without associated hepatic lesions indicates aspiration of infected ammotic fluid on inhalation of tubercle bacilli.*

  *Lungs are the most common organs involved in congenital tuberculosis being involved almost all cases.*
- Congenital Tuberculosis is charachterized by a nonimmune, non reactive response with abundant caseation and an unsually large number of bacilli. There may be multiple foci of infection within the primary site and the distribution is usually miliary.

**127. Answer is B (Haematogenous Spread):** *Thurlbeck's Pathology of the Lung (Thieme) 2005/223; Avery's Diseases of the New-born/ (Lippincott) 8th/543, 543, 544, 545; Oski's Pediatrics 4/h/1151; Liver Disease in Children (Cambridge University Press 2007/876)*

***Primary Complex in Liver in cases of Congenital Tuberculosis occurs when infection enters the fetus through the umbilical veins (Trans-placental; Haematogenous Infection).***

- *Liver is the most common Primary site of infection in* Congenital Tuberculosis caused by ***Trans-placental*** or Haematogenous route
- *Lung is the most common Primary site of infection* in Congenital Tuberculosis caused by ***aspiration of infected amniotic fluid***
- *Gastrointestinal Tract is the most common Primary site of infection* in Congenital Tuberculosis caused by ***ingestion of infected amniotic fluid***

| |
|---|
| *Since Lungs are eventually involved in most cases of congenital tuberculosis where Liver is the primary site of infection, Lungs are overall the most commonly involved sites in Congenital Tuberculosis* |

**128. Ans. Answer is A (Lungs):** *Textbook of Pulmonary Medicine by Behera' 2nd/495*

***The most common organ involved in congenital tuberculosis are the Lungs followed by Liver.***

*'The form of disease is usually miliary with multiple organ involvement. Lungs are involved in almost all cases. Other sites frequently involved are liver, spleen, lymph nodes, the gastrointestinal tract and kidney'.*
*-Textbook of Pulmonary Medicine by Behera 2nd/495*

**129. Answer is D (Monotoux is always positive):** *Harrison 18th/p1349 Harrisons 17th/1013 Harrisons 11th/629*

***Montoux test is not always positive in cases of Miliary Tuberculosis.***

***It may be negative /non reactive as a result of anergy.***
**Miliary Tuberculosis may occur following primary infection and secondary reactivation**

*Miliary tuberculosis is due to hematogenous dissemination of tubercle bacilli.*
*'Classically miliary tuberculosis develops following hematogenous dissemination at the time of primary infection' - Harrisons 11th/629*

*'In adults miliary tuberculosis may be due to reactivation of old disseminated foci (secondary reactivation)'*
*- Harrisons 17th/1013*

**Sputum microscopy is usually negative (Harrisons 17th/1013)**
*'Sputum smear microscopy is negative in 80% of cases' – Harrison 17th/1013*
**Montoux test is negative in 20-30% of patients with Miliary Tuberculosis**
*'The Tuberculn skin Test (montoux) may be non reactive due to anergy' -Nelson 5th/567*

*'Tubercular anergy is common in Miliary Tuberculosis and a negative skin test should not be a deterrant to the consideration of this diagnosis' - Harrison 11th/629*

*'Upto 30% of children have a negative tuberculin skin test' - 'Tuberculosis : Current concepts and Treatment' 2nd/201*

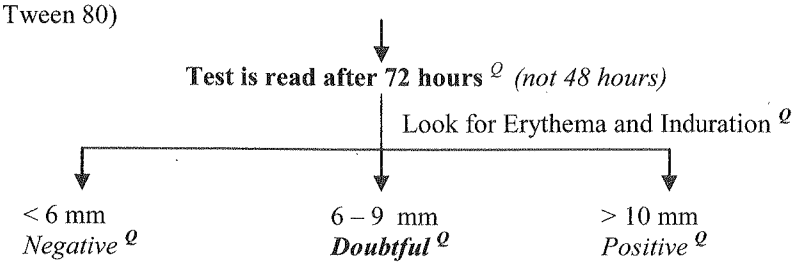
**Liver, kidney and spleen are common sites of involvement along with other sites**
*Almost every organ in the body may be involved. Miliary tuberculosis is most prominent in Liver, spleen, kidney and other organs including bone marrow, adrenals, meninges, fallopian tubes and epididymis - Robbins 7th/386*

**130. Answer is C (A positive test does not .....):** *Park*

***A positive test indicates that patient is infected with M. tuberculosis. It does not however prove that the person is 'suffering' from the disease – Park***

**Montoux test**

Montoux test is carried out by injecting one tuberculin unit (1TU) of PPD in 0.1 ml on the flexor surface of forearm (PPD RT 23 with Tween 80)




- ***A positive test indicates that patient is infected with M. tuberculosis. It does not however prove that the person is 'suffering' from the disease*** – *Park*
- ***Studies indicate that 92% of new cases occur in persons who already are tuberculin reactors***.– *Park*
- ***6-9 mm induration does not indicate high chances of developing tuberculosis.*** Infact patients with 25 mm induration have more chances of developing tuberculosis than those with 6-9 mm induration - *Park*

**131. Answer is D (Atypical mycobacterial infection):** *Ananthnarayan 6th / 333; Park 18th/150*

***Infection with atypical mycobacteria or other related mycobacteria are associated with false positive reactions and not false negative tests.***

False negative tuberculin tests (Anergy) may occur in situations such as :

- *Miliary tuberculosis* ℚ
- Convalescence from some viral infections like *Measles* ℚ
- Lymphoreticular malignancy
- *Sarcoidosis* ℚ
- *Severe malnutrition* ℚ
- *Immunosuppressive therapy* ℚ
- *Defective cell mediated immunity* ℚ

**132. Answer is E (All of the above):** *Harrison 18th/p 1350, 1351 Harrisons 17th/1014,1015*

***Montoux testing, sputum for AFB, PCR and BACTEC (culture method) may all be used fo establish the diagnosis of Tuberculosis.***

**133. Answer is A (Pulmonary tuberculosis):** *CMDT 2005/ 254; 2009/246*

***All features mentioned in this question are in favour of pulmonary tuberculosis and the only feature that troubles is a 'negative sputum cytology'. A negative sputum cytology however does not rule out pulmonary tuberculosis.***
***'A negative sputum cytology does not rule out pulmonary tuberculosis'***- *CMDT*

*'There is a definite set for patients of 'suspected TB with negative sputum smears'. These patients are usually investigated by bronchoscopy as the next diagnostic step. Bronchial washings and transbronchial lung biopsies are specially helpful and increase the diagnostic yield'. – CMDT*

**Definitive diagnosis of TB :**
***Does* not depend on sputum cytology** but, ***it depends on recovery of Mycobacterium TB in cultures or identification of organism by DNA probe.***

**Remember:** ***"demonstration of acid fast bacilli on sputum smears does not confirm a diagnosis of TB"***.

Since saphrophytic and non tuberculous mycobacteria make colonize the airways or cause pulmonary disease.
***It is sputum culture with demonstration of M. TB that is diagnostic.***

**134. Answer is B (Tuberculosis) :** *Harrison 17th/2020, 1523, 956; 15th/1969, 1470, 1024, 1025, 1027*

***Most common cause of necrotic lymph nodes with peripheral rim enhancement is tuberculosis.***

- **Peripheral rim enhancement is seen in most granulomatous lymphadenopathies.**
  **Most common cause of necrotic lymph nodes with peripheral rim enhancement is Tuberculosis**
  - In tuberculosis affected lymph nodes show relatively low attenuation of their central region and peripheral rim enhancement after I.V. contrast material
  - In Sarcoidosis lymph nodes are **not necrotic** and **calcification is uncommon**
- ***Expectoration*** is a major manifestation in tuberculosis.
  *It is usually not associated sarcoidosis, silicosis and lymphoma.*
- ***Cough and bilateral upper lobe fibrosis*** makes lymphoma unlikely. It may be seen in the other conditions.

*The only condition satisfying all the clinical features mentioned in the question is tuberculosis and hence is the answer of choice.*

**135. Answer is B (Tuberculosis) :** *Refer previous question*

***Most common cause of necrotic lymph nodes with peripheral rim enhancement is Tuberculosis.***

**136. Answer is B (Pulmonary Artery):** *'Churchill Livingstone Medical Dictionary' by Brooker 16th/410; 'Step by Step Computed Tomography' by Karthikeyan & Chegu (Jaypee) 2004 /134*

***Rasmussen's aneurysm refers to an aneurysm of the pulmonary artery within/adjacent to a tuberculous cavity***

**Rasmussen's aneurysm**

- This is an aneurysm *arising from the pulmonary artery*
- This is typically a *'pseudoaneurysm'* resulting from inflammatory necrosis of the vessel wall, by *direct invasion* of the pulmonary arterial wall by adjacent tuberculous infection
- Typically the vessel injury occurs in the *upper lobes* of sites of pulmonary tuberculosis
- Rupture of these aneurysms results in *hemoptysis and pulmonary hemorrhage*

**137. Answer is E (All of the above):** *'Infection Control In The community' by Lawrence & May 1st (2003)*

***All of the options require consideration for a diagnosis of MDR – TB.***

**Mult Drug Resistant Tuberculosis (MDR TB)**
MDR-TB is defined by the presence of resistance to both Rifampicin and Isoniazid with or without other resistance

MDR TB should be considered in patients with:

- *Previous drug treatment for tuberculosis*
- *Contact with a case of known MDRTB*
- *HIV infection*
- *Failure of clinical response on treatment*
- *Prolonged sputum smear or culture positive while on treatment (smear positivity at 4 months or culture positivity at 5 months)*

**138. Answer is B (INH and Rifampicin):** *Harrison 18th/ 1373*

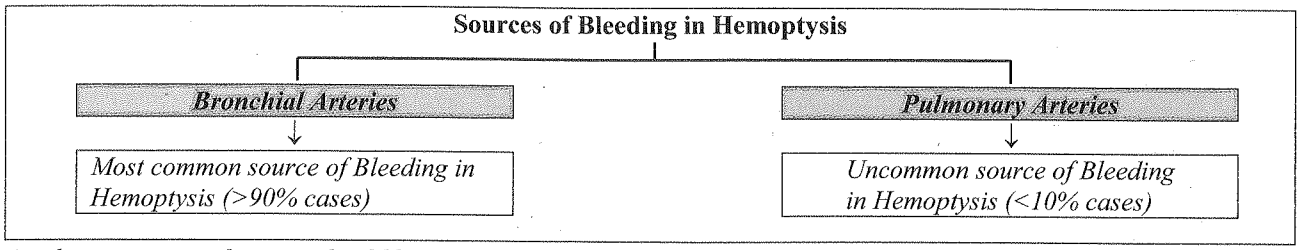
***Multi-Drug Resistant Tuberculosis is defined by resistance to INH and Rifampicin.***

*'Multi-Drug Resistant Tuberculosis (MDR-TB) is defined as disease caused by strain of M. Tuberculosis that is resistant to both Isoniazid (INH) and Rifampicin – the most efficacious of the first line Anti-TB drugs' –Harrison*

**139. Answer is B (Bronchial Artery):** *Harrison 18th/p 284 Harrisons 17th/227; Harrisons 16th/207; Diagnosis and treatment of symptoms of Respiratory; Vascular and Interventional Radiology by bakal (2002)/158*

***Hemoptysis usually arises from the bronchial arteries. Pulmonary arteries are a rare source of hemorrhage. The vascular structure that should be evaluated first for angiographic treatment are therefore bronchial arteries.***

*'Majority of cases of hemoptysis represent bleeding from the bronchial arteries, therefore bronchial angiography is usually the initial angiographic procedure'-Diagnosis and Treatment of symptoms of the Respiratory Tract (2007)/177*




*A pulmonary arterial source should be considered in addition to the more common systemic source (bronchial artery) in the setting of destructive lung lesion such as cavitatory tuberculosis. However the vascular structure that should be evaluated first is the bronchial artery.*

**Remember : Ramussen Aneurysm**

- Ramussen aneurysm is a rare cause of bleeding in cavitatory tuberculosis and results from erosion of tuberculous cavity into a pulmonary artery branch.
- *The most common source of bleeding in Remussen aneurysm is the pulmonary artery*[Q].

## Sarcoidosis

**140. Answer is A (Sarcoidosis):** *Harrison 18th/p 2806, 2807, 2808 Harrison 14th/1927, 1923, 15th/1971, 1969; Harrisons 16th/ 2017, 2018, 2023; Harrison 17th/2136, 2137*

***The presence of non-caseating granuloma, along with bilateral hilar lymphadenopathy, goes strongly in favour of a diagnosis of Sarcoidosis'.***

**Sarcoidosis:** *Review*

Sarcoidosis is a chronic multisystem disorder of unknown cause characterized by accumulation of T lymphocytes and mononuclear phagocytes in various tissues of body

Non caseating **SAR**coid granulomas in affected organs

| Lung (90%) | Lymph nodes (75-90%) | Skin | Others |
|---|---|---|---|
| • ***Interstitial lung disease***[Q]<br>- Fibrosis of lung parenchyma<br>• Pleura is involved in 1-5% of cases u/e ***pleural effusion***[Q]<br>• *Cavitation* ***is rare***[Q] | • B/L hilar lymphadenopathy is the hallmark of sarcoidosis<br>• Parotid enlargement B/e involvement is the vuli | • ***Erythema nodosum***[Q]<br>• ***Lupus perenium***[Q] (purple blue shiny swollen lesions on nose, cheeks, lips, ears). | Eye: Uveitis<br>Kidney (rare): Renal hypercalcemia with or without hypercalcuria<br>Skeletal: Arthritis<br>Nervous system: Peripheral neuropathy.<br>Heart: Cor pulmonle |

**Sarcoid granulomas**: The inflammatory process in sarcoidosis is characterized by formation of sarcoid granulomas in various organs. – *Harrisons 16th/ 2018*

Giant Cells within granulomas can be of Langerhan's or Foreign body variety and often contain inclusions bodies:

Inclusions seen in giant cells in sarcoidosis. (Remember as **SAR**coidosis)

- ***S**chaumann bodies*[Q]
- ***A**steroid bodies*[Q]
- ***R**esidual bodies*[Q]

**141. Answer is A (Often cavitate) :** *Harrison 18th/2807; 15th/1971; Harrison 16th/2020, 2023; Harrison 17th/2136, 2137*

***Cavitation is uncommon seen only in less than 5% of patients with sarcoidosis.***

- Of individuals with **sarcoidosis** 90% have abnormal findings on chest x ray Sarcoidosis of the lung is primarily an interstitial lung disease in which the inflammatory process involves the alveoli, small bronchi and small blood vessels. **Cavitation is seen in <5% patients with sarcoidosis**.- Harrisons 16th-2020
- B/e hilar lymphadenopathy is the hallmark of disease – Harrisons 16th/2023

**The three classic x-ray pattern of pulmonary sarcoidosis are**
- ***Type I*** : *B/L hilar lymphadenopathy with no parenchymal changes*
- ***Type II*** : *B/L hilar lymphadenopathy with diffuse parenchymal changes*
- ***Type III*** : *Diffuse parenchymal change with no hilar lymphadenopathy.*

- Sarcoidosis has a variable course. Disease clears spontaneously in 50% of patients – *Harrisons 16th/2023*
- Tuberculin test may be negative due to the presence of skin anergy – *Harrisons 16th/2023*

**142. Answer is A (Lung):** *Harrison*

***The most common organ involved in Sarcoidosis is the Lung****. Pulmonary involvement, found in over 90 percent of sarcoidosis patients, is the most frequent manifestation of the disease.*

**143. Answer is A (CD4/CD8 counts in the blood):** *Harrison 15th/1970; Harrison 16th/2017-2023; Not in Harrison 17th*

*The patient in question is suffering from sarcoidosis. CD4/CD8 Counts in Sarcoidosis are typically increased in the affected organs but not in the blood*

'***While there is marked enhancement of no. of TH cells at the sites of disease the number of TH cells in the blood are normal****. Where as TH cells in the involved organs are proliferating at an enhanced rate the T cells in other sites such as blood are quiescent' - Harrison*

It is the CD4 / CD8 counts in the affected organs which is an important ancillary aid in established the diagnosis of sarcoidosis and not the CD4 / CD8 count in the blood as specifically asked in the question.

Active sarcoidosis results from an exaggerated cellular immune response resulting in accumulation of large no. of T4 cells in the affected organs, where the ratio of CD4 to CD8 cells may be as high as 10:1.
Although CT of chest is also only rarely helpful, it may identify early fibrosis and active alveolitis and thus contribute to a diagnosis of sarcoidosis.

**Diagnostic tests for sarcoidosis have often been asked**

Diagnostic tests

| Ancillary | Confirmatory |
|---|---|
| - Blood: ***ACE***[Q]<br>- ***X ray chest***[Q]<br>- ***Skin test for anergy***[Q]<br>- ***Gallium 67 etc.***[Q] | BIOPSY |

1. ***X-Ray chest***:
   - Bilateral hilar lymphadenopathy is the hallmark of disease
   - Parenchymal involvement may or may not be present ***(clear lung fields)***[Q]
   - ***Egg shell calcification of hilar nodes may be seen***[Q]
   - ***Lambda sign or Panda Sign***
   - ***Garland's Triad***
2. ***Kveim siltzbach test***[Q]***: Skin test***[Q]:
   - intradermal injection of a heat treated suspension of a sarcoidosis spleen extract.
3. ***Angiotensin converting enzyme (ACE) in blood***[Q]:
   - ACE is elevated in 2/3 of patients with sarcoidosis [Q] (60%) [Q]
   - ACE levels indicate activity of disease [Q]
   - ACE levels provide an important method of monitoring the course of disease.[Q]

   *(The cells in granuloma release angiotensin converting enzyme into the serum)*
4. ***Gallium 67 scan***: Gallium 67 lung scan is usually abnormal showing a pattern of diffuse uptake
5. ***Bronchoalveolar large:*** Lavage fluid is characterized by
   - increase in Lymphocytes[Q]
   - high CD4 / CD8 cell ratio[Q]
6. ***Biopsy***:
   - Biopsy is mandatory to make a definitive diagnosis of sarcoidosis
   - Characteristic finding is a typical non casseating granuloma[Q]
7. ***Lung function abnormalities***: Typical for interstitial lung disease.

**144. Answer is B (Sarcoidosis)**

*Kviem Siltzbach test is a specific diagnostic test used for the diagnosis of Sarcoidosis.*

**Kviem Siltzbach test**

*Specifically prepared tissue derived from the spleen of a patient suffering from Sarcoidosis is injected intra-dermally into the patient with suspected Sarcoidosis. A biopsy is performed 4-6 weeks after the injection. The presence of non-casseating granulomas in the biopsy specimen is highly specific for the diagnosis of sarcoidosis*

**145. Answer is A (Sarcoidosis):** *Harrison 17th/ 2149; Top 3 Differentials in Radiology: A Case Review (Thieme), 2011/561*

***Lambda Sign and Panda sign on Gallium scan are typically described for Sarcoidosis***

*Active pulmonary and/or mediastinal Sarcoidosis is gallium avid and a positive gallium scan can support the diagnosis of Sarcoidosis. Typical patterns of uptake have been described as 'panda' and 'lambda' signs.*

| | |
|---|---|
| *Lambda Sign* | *Formed from increased uptake in bilateral hilar and right paratracheal nodes* |
| *Panda Sign* | *Formed from increased uptake in the parotids and lacrimal glands* |

***A Lambda sign in combination with a so-called Panda sign (Lambda-Panda Sign) is a highly specific pattern for Sarcoidosis.***

*The degree of uptake typically depends on the activity of disease and gallium scan is positive only in the setting of active parenchymal disease and negative in remission*

**146. Answer is D (Left pretracheal lymph nodes):** Chest Radiology: The Essentials 2nd/ 165

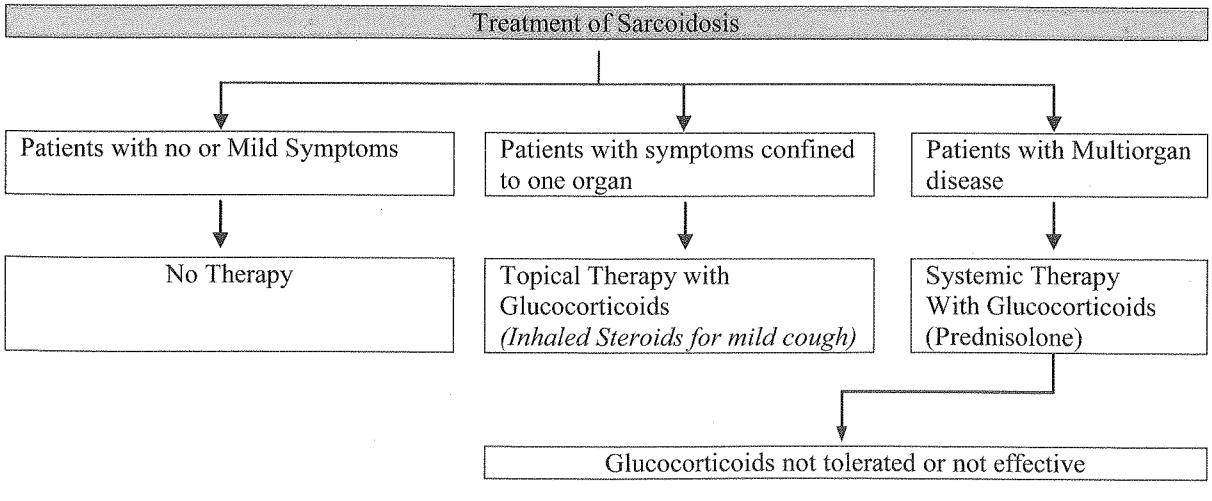
***Bilateral hilar lymphadenopathy with with right paratracheal nodal enlargement is classic for sarcoidosis and is referred to as the 1-2-3 sign or Garland triad.***

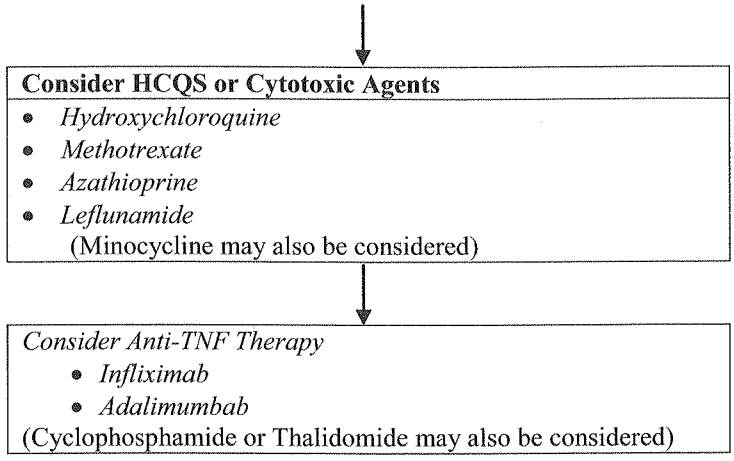
| Garland's triad (also known as the 1-2-3 sign or Pawnbrokers sign) of Sarcoidosis |
|---|
| • Right paratracheal nodes<br>• Right hilar nodes<br>• Left hilar nodes |

**147. Answer is A (Prednisolone):** *Harrison 18th*

***Prednisolone (Corticosteroid) is the treatment of choice for both acute and chronic phase of Sarcoidosis that requires treatment***

*Corticosteroid medications are considered the first line of treatment for sarcoidosis that requires therapy. Systemic corticosteroids effectively reduce systemic inflammation in most people, thereby slowing, stopping or even preventing organ damage.*








## Pulmonary Edema

**148. Answer is D (>25mm Hg):** *Differential Diagnosis in Internal Medicine: From Symptom to Diagnosis (Thieme, 2011)/630; Respiratory Care Anatomy and Physiology: Foundations for Clinical Practice (Elsevier Health Sciences, 2013)/ 126*

***Alveolar Pulmonary edema from elevated hydrostatic pressure (Cardiogenic) is typically associated with PCWP >25 mm Hg.*** *Elevated PCWP but with Pressure <25mm Hg is usually associated with interstitial pulmonary edema and not true alveolar pulmonary edema.*

**Hydrostatic pulmonary edema** is also known as cardiogenic pulmonary edema (since it typically arises from left heart failure). The inefficient left ventricle causes blood to back up in the pulmonary circulation, *increasing hydrostatic pressure* in the pulmonary capillaries (Increased PCWP).
High capillary pressure progressively forces fluid first into the interstitium (Interstitial Pulmonary Edema) and then into the alveoli (Alveolar Pulmonary Edema).

Three stages of pulmonary edema can be distinguished based on the degree of fluid accumulation
- Stage 1 is characterized by excess fluid that can still be cleared by lymphatic drainage.
- Stage 2 is characterized by the presence of interstitial edema.
- Stage 3 is characterized by alveolar pulmonary edema (fluid and proteins enter the alveolar space)

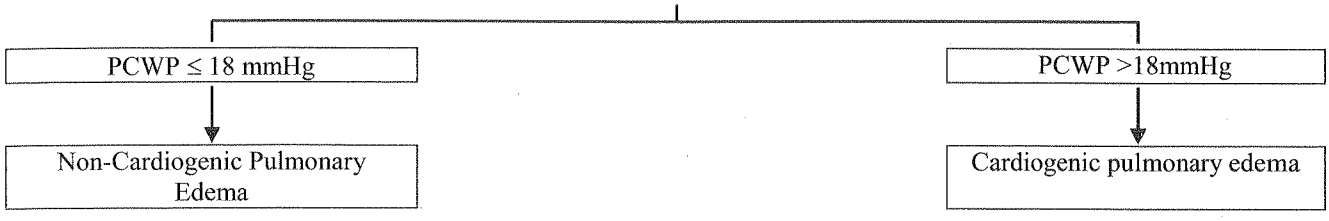
| PCWP | Stage | Interpretation in relation to Hydrostatic Pulmonary Edema |
|---|---|---|
| 6-12 mm Hg (Normal) | Normal | No Pulmonary Edema |
| 12-18mm Hg (Mild Increase) | Stage I | Usually not associated with pulmonary edema<br>Excess fluid can still be cleared by lymphatic drainage<br>No Physical or X-ray Findings are usually evident |
| 18 – 25 mm Hg (Moderate Increase) | Stage 2 | Characterized by the presence of interstitial edema<br>Some physical findings including some fine crackling breath sounds may be evident<br>X-ray evidences of pulmonary edema in the form of engorged pulmonary vessels and appearance of infiltrates may be seen |
| >25 mm Hg (Severe Increase) | Stage 3 | Characterized by alveolar pulmonary edema (fluid and proteins enter the alveolar space)<br>Physical findings are prominent and include clinically significant hypoxemia, tachypnea, respiratory distress, diffuse crackles, and wheezing breath sounds<br>Obvious x-ray evidence of pulmonary edema (greatly increased infiltrates and vascular engorgement) |

**149. Answer is A (6-12 mm Hg):** *Harrison 18th/ 2235*

*The normal Pulmonary Capillary Wedge Pressure is between 6 to 12 mmHg.*

**Pulmonary capillary wedge pressure (PCWP)**
**(Normal = 6 to 12 mm Hg)**

PCWP is recorded when the PA catheter balloon is inflated and wedged in a branch of the pulmonary artery.
PCWP reflects left atrial pressure
When there is no obstruction between the left atrium and ventricle PCWP =left atrial pressure = left ventricular end-diastolic pressure)
**PCWP normally ranges from 6 to 12 mm Hg**




**150. Answer is D (25 mm Hg):** *Differential Diagnosis in Internal Medicine: From Symptom to Diagnosis (Thieme, 2011)/630; Respiratory Care Anatomy and Physiology: Foundations for Clinical Practice (Elsevier Health Sciences, 2013)/ 126*

*Severe Pulmonary Edema is seen when PCWP rises above 25mm Hg.*

| Hydrostatic Pulmonary Edema and PCWP | Interpretation |
|---|---|
| 6-12 mm Hg (Normal) | No Pulmonary Edema |
| 12-18mm Hg(Mild Increase) | May or may not be associated with Pulmonary Edema (Early Interstitial pulmonary edema may be seen ) |
| 18 – 25 mm Hg (Moderate Increase) | Usually associated with Interstitial Pulmonary Edema |
| >25 mm Hg (Severe Increase) | Usually associated with Alveolar Pulmonary Edema |

## Adult Respiratory Distress Syndrome (ARDS)

**151. Answer is D (ARDS):** *Harrison 17th /1680; Robbins 7th/715*

***Shock lung is a synonym used for Acute/Adult Respiratory Distress syndrome.***

**Synonym: for ARDS** *(Taken from 'Pathology of Lung')*

- *Shock lung*
- *Blast lung*
- *Traumatic wet lung*
- *Congestive Atelectasis*
- *DoNang Lung*
- *Noncardiogenic Pulmonary Edema*
- *Diffuse Alveolar Damage*

**152. Answer is C (Diffuse Alveolar Damage)**

*Diffuse Alveolar Damage is the histopathological hallmark of Acute Respiratory Distress Syndrome or Shock Lung*

*Diffuse Alveolar Damage and Shock Lung are used as synonyms of ARDS*

**153. Answer is None or C (Cardiopulmonary bypass with heart lung machine):** *Harrison 18th/p 2205 Harrison 16th/1592; 17th /1680 API 7th/1240*

*Cardiopulmonary bypass is a cause for indirect lung injury while the rest three cause direct injury to lungs. Although all four options may cause acute lung injury, the single best answer of exclusion would be cardiopulmonary bypass.*

**Clinical disorders associated with lung injury/ ARDS**

| Direct lung injury | Indirect lung injury |
|---|---|
| • Pneumonia<br>• Aspiration of gastric contents<br>• Pulmonary contusion<br>• Near drowning<br>• Toxic inhalation injury | • Sepsis<br>• Severe trauma: - Multiple bone fractures<br>- Head trauma<br>- Flail chest<br>• Burns<br>• Multiple transfusions<br>• Drug overdose: eg Narcotic overdose<br>• Pancreatitis<br>• Post-cardiopulmonary bypass |

**154. Answer is B (High Altitude):** *Harrison's 16th/ 1592; Harrison 17th/ 1680; API 7th/ 1240*

*Pulmonary edema with normal pulmonary capillary wedge pressure suggests a diagnosis of ARDS or non cardiogenic pulmonary edema.*

*High altitude has been grouped as one of the miscellaneous causes for ARDS, reflecting pulmonary oedema with a normal PCWP - API 7th/ 1240*

| Some miscellaneous causes for ARDS |
|---|
| • Renal failure |
| • Liver failure |
| • Disseminated intravascular coagulation |
| • Ecclampsia |
| • Amniotic fluid emboli / Air emboli |
| • Hanging |
| • High altitude |

**155. Answer is B (High Altitude):** *Refer text below*

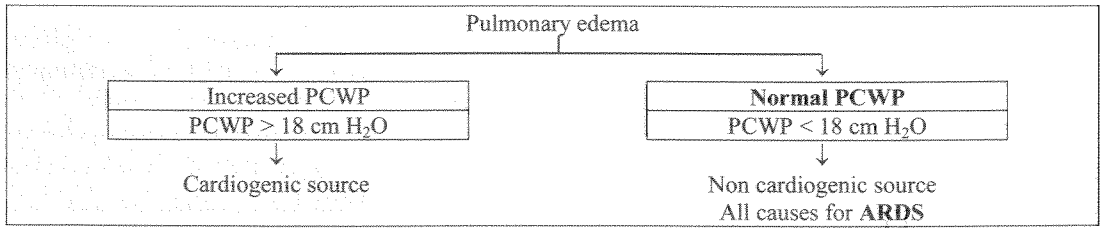
*Pulmonary Edema with a Normal PCWP suggests a diagnosis of Non-Cardiogenic Pulmonary Edema as may be seen in High Altitude.*
*Cardiogenic Pulmonary Edema (Left Atrial Myxoma; Mitral Stenosis; LVF) is typically associated with a raised PCWP.*

**156. Answer is D (All of the above):** *Harrison 18th/p 2205 Harrisons 17th/1680; 16th/1592*

*Acute Pancreatitis, Trauma and severe Falciparum malaria may all lead to ARDS*

**157. Answer is A (Narcotic overdose):** *Read text below*

*Pulmonary edema with normal pulmonary capillary wedge pressure suggests a diagnosis of ARDS or non cardiogenic pulmonary edema. Narcotic overdose is the only non cardiogenic cause for pulmonary edema (ARDS) amongst the options provided and hence the answer here.*



**158. Answer is A (Diffuse Alveolar Damage):** *Harrison 18th/2205, 2206, 2207*

***Diffuse Alveolar Damage (DAD) is the histopathological hallmark of Acute Respiratory Distress Syndrome (ARDS) and the most characteristic feature amongst the options provided. Diffuse Alveolar Damage is often used as a synonym for ARDS.***

*'The pathological hallmark of ARDS is Diffuse Alveolar Damage'*
*– Thoracic Imaging (Thieme) 2010/Case 78*

*'The histological hallmark of ARDS is Diffuse Alveolar Damage'*
*– 'Intensive Critical Care Medicine' (Springer) 2009/210*

| Synonyms for ARDS |
|---|
| • ***Diffuse Alveolar Damage*** |
| • *Shock Lung* |
| • *Blast Lung* |
| • *Traumatic Wet Lung* |
| • *Congestive Atelectasis* |
| • *Do Nang Lung* |
| • *Noncardiogenic Pulmonary Edema* |
| *Taken from 'Pathology of the Lung'* |

## ARDS (Acute Respiratory Distress Syndrome)

**Diffuse alveolar damage (ARDS)**
Alveolar closure and collapse
(Exaggerated by reduction in surfactant due to injury to type II pneumocytes)
↓
***Reduced compliance*** of Lung as a whole $^{Q}$
(*Stiff lung*)
↓
***Diminished tidal volume*** $^{Q}$
Worsened gas exchange
(Pulmonary edema + Hyaline membrane (fibrin + coagulated cell debris)
***Hypoxemia*** $^{Q}$
↓
Increased Respiratory frequency
↓
$CO_2$ washout and ***Hypocapnia***

**ARDS is an acute form of lung injury characterized by:**
- Increased permeability of alveolar capillary membrane.
- ***Diffuse alveolar damage.***
- Accumulation of proteinaceous pulmonary edema (non cardiogenic pulmonary edema $^{Q}$)

### Features of ARDS

| Clinical /Physiological |
|---|
| • Clinical history of insult known to cause ARDS |
| • Clinical exclusion of chronic lung disease and Left ventricular failure |
| • ***Diffuse alveolar damage.*** |
| • *Reduced surfactant (Injury to type II pneumocytes)* |
| • Increased permeability of alveolar capillary membrane. |
| • Accumulation of *proteinaceous pulmonary edema* (non cardiogenic pulmonary edema $^{Q}$) |
| • Pulmonary edema + ***Hyaline membrane*** (fibrin + coagulated cell debris) |
| • ***Reduced compliance*** (*stiff lung*) |
| • ***Diminished tidal volume*** $^{Q}$ |
| • ***Hypoxemia*** $^{Q}$ (Worsened gas exchange d/t ***pulmonary shunting***) |
| • ***Hypocapnia*** $^{Q}$ ($CO_2$ washout) |

| Diagnostic Criteria (ARDS) | |
|---|---|
| $PaO_2/FiO_2$ | *≤200 mm Hg* |
| Onset | *Acute* |
| Chest Radiograph | *Bilateral Alveolar or Interstitial infiltrates* |
| Absence of Left Atrial Hypertension | • *PCWP≤18 mmHg*<br>• *No clinical evidence of increased left atrial pressure* |

**159. Answer is C (Hypercapnia):** *Harrison 18th/p 2205, 2206, 2207; Harrison 15th/ 1524; Harrison 16th/ 1592; Harrison 17th/ 1680, 1681*

***ARDS results in Type I Respiratory failure and is characterized by normal or low $PaCO_2$ (Hypocapnia) and not Hypercapnia*** *(see previous explanation on types of respiratory failure).*

## ARDS (Acute Respiratory distress syndrome)

**ARDS is an acute form of lung injury characterized by:**

- Increased permeability of alveolar capillary membrane.
- Diffuse alveolar damage.
- Accumulation of proteinaceous pulmonary edema (non cardiogenic pulmonary edema $^{Q}$)

Diffuse alveolar damage (ARDS)
Alveolar closure and collapse
(exaggerated by reduction in surfactant due to injury to type II pneumocytes)
↓
***Reduced compliance*** of Lung as a whole $^{Q}$
(*stiff lung*)
↓
***Diminished tidal volume*** $^{Q}$
Worsened gas exchange
(pulmonary edema + Hyaline membrane (fibrin + coagulated cell debris)
***Hypoxemia*** $^{Q}$
↓
Increased Respiratory frequency
↓
$CO_2$ washout and ***Hypocapnia*** $^{Q}$

**160. Answer is D (Hypercapnia):** *Harrison 18th/p 2205, 2206, 2207; Harrison 17th/ 1680, 1681*

***ARDS results in Type I Respiratory failure and is characterized by normal or low $PaCO_2$ (Hypocapnia) and not Hypercapnia.*** *Reduced compliance (Stiff lung), Hypoxemia and Non-Cardiogenic Pulmonary Edema are typical features of ARDS.*

**161. Answer is D (Hypercapnia):** *Refer previous question*

***ARDS results in type I Respiratory failure and is characterized by normal or low $PaCO_2$ (Hypocapnia) and not hypercapnia.***

**Pulmonary Shunting:** Significant shunt occurs in ARDS where pulmonary arterial blood shunts past flooded and collapsed Alveoli into pulmonary veins. Shunting of the poorly oxygenated venous blood into arterial circulation significantly contributes to arterial hypoxemia.

**Reduced compliance:** Reduced lung compliance and stiff lung are characteristic features of ARDS

**Hypoxemia:** Arterial hypoxemia is a characteristic feature of ARDS and may be caused by reduced lung compliance and pulmonary shunting.

**Features of ARDS**

| Clinical /Physiological |
|---|
| • Clinical history of insult known to cause ARDS |
| • Clinical exclusion of chronic lung disease and Left ventricular failure |
| • ***Diffuse alveolar damage.*** |
| • *Reduced surfactant (Injury to type II pneumocytes)* |
| • Increased permeability of alveolar capillary membrane. |
| • Accumulation of *proteinaceous pulmonary edema* (non cardiogenic pulmonary edema $^{Q}$) |
| • Pulmonary edema + ***Hyaline membrane*** (fibrin + coagulated cell debris) |
| • ***Reduced compliance*** (*stiff lung*) |
| • ***Diminished tidal volume*** $^{Q}$ |
| • ***Hypoxemia*** $^{Q}$ (Worsened gas exchange d/t ***pulmonary shunting***) |
| • ***Hypocapnia*** $^{Q}$ ( $CO_2$ washout) |

| Diagnostic Criteria (ARDS) | |
|---|---|
| $PaO_2/FiO_2$ | *≤200 mm Hg* |
| Onset | *Acute* |
| Chest Radiograph | *Bilateral Alveolar or Interstitial infiltrates* |
| Absence of Left Atrial Hypertension | • *PCWP≤18 mmHg*<br>• *No clinical evidence of increased left atrial pressure* |

**162. Answer is D (Hypercapnia):** *Harrison 18th/2205; Harrison 16th/1592; 17th/ 1680, 1681API 7th/1240; Refer question on Respiratory failure*

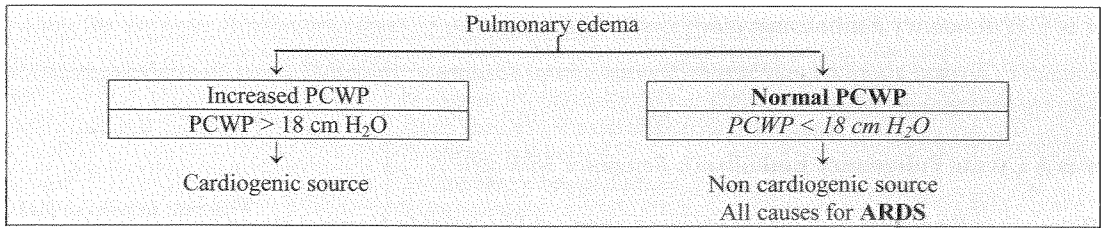
***ARDS or Adult respiratory distress syndrome is a condition characterized by Acute Hypoxemic Type I Respiratory failure due to pulmonary edema caused by increased permeability of the alveolar capillary barrier.*** *It is thus associated with Hypoxemia but not with Hypercapnia.(Refer question on respiratory failure)*

**163. Answer is B (Hypercapnia):** *Harrison 17th /1680, 1681*

*ARDS results in Type I Respiratory failure and is characterized by normal or low $PaCO_2$ (Hypocapnia) and not Hypercapnia (see previous explanation on types of respiratory failure).*

**164. Answer is C (Increased Left atrial pressure):** *Repeat; Refer previous question*

*ARDS is characterized by a PCWP of ≤ 18mm Hg with no clinical evidence of increased left atrial pressure.*




**165. Answer is A (Diffuse Alveolar Damage):** *Harrison 18th/p 2205 Robbins 7th/715; Harrisons 17th/1680*

*'Shock lung' is a synonym used for Acute Respiratory Distress Syndrome.*
*Diffuse alveolar damage is a characteristic feature of ARDS/Shock lung and is also often used as a synonym for ARDS.*

**166. Answer is A ($PaO_2/FiO2$)>200 mmHg):** *Harrison 18th/p 2205 Harrisons 17th/1680*

*'Acute Lung Injury' is a milder disorder than ARDS and is characterized by $PaO_2/FiO_2$ of less than 300 mm Hg.*

| Diagnostic Criteria | ALI | ARDS |
|---|---|---|
| $PaO_2/FiO_2$ | *≤300 mm Hg* | *≤200 mm Hg* |
| Onset | *Acute* | *Acute* |
| Chest Radiograph | *Bilateral Alveolar or Interstitial infiltrates* | *Bilateral Alveolar or Interstitial infiltrates* |
| Absence of Left Atrial Hypertension | • *PCWP≤ 18 mmHg*<br>• *No Clinical evidence of increased left atrial pressure* | • *PCWP≤18 mmHg*<br>• *No clinical evidence of increased left atrial pressure* |

*ALI is a less severe disorders than ARDS but has the potential to evolve into ARDS. ALI can be differentiated from ARDS by the arterial $PO_2/FiO_2$ (Inspiratory $O_2$ fraction) ratio.*

**167. Answer is D (PaO2/FIO2 ≤ 200):** *Harrison 18th/2207; 17th/1681; Harrisons 16th/1592; Ref. Previous question*

*ALI is associated with a PaO2/FIO2 ≤ 300 and not PaO2/FIO2 ≤ 200*
***Bilateral alveolar interstial infiltrates on Radiographs along with, hypoxemia and pulmonary shunting due to intra alveolar filling are characteristic features of both ALI and ARDS.***

## Pulmonary Thromboembolism

**168. Answer is A (Pulmonary thromboembolism):** *Harrison 18th/p 2172 Harrison 15th/ 1508, Harrison 16th/ 1561; Harrison 17th/ 1651, 1652*

*Sudden onset of dyspnea and chest pain following surgery or immobilization, strongly suggests a diagnosis of pulmonary thromboembolism.*

**Remember:**
- The most frequent symptom of PE is dyspnea [Q]
- The most frequent sign of PE is tachypnea [Q]

| Symptoms suggesting massive PE | Symptoms suggesting small emboli located distally |
|---|---|
| Dyspnea | Pleuritic pain |
| Syncope | Cough |
| Hypotension | Haemoptysis |
| Cyanosis | |

**169. Answer is A (Chest pain is the most common symptom):** *Harrison 18th/p 2172 Harrison 15th/ 1509; 16th/ 1561; 17th/ 1651, 1652*

***'Dyspnea is the most frequent symptom of PE and tachypnea is the most frequent sign'–Harrisons 16th/1561***

Chest pain is due to pulmonary infarction and usually indicates a small PE located distally near the pleura.

**170. Answer is C (Pulmonary Embolism):** *Harrison 18th/2172*

***Sudden onset of Dyspnea and Chest Pain following injury, surgery or immobilization strongly suggests a diagnosis of pulmonary thromboembolism.***

**171. Answer is A (Acute Pulmonary Embolism):** *Reference with text*

***Acute Pulmonary Embolism is the most common cause of Preventable Hospital Death.***

*'Acute Pulmonary Embolism is the most common cause of preventable Hospital Death'*
*- 'The 5 minute ICU consult / Lippincott Williams/2012/384*

*'Pulmonary embolism is the most common preventable cause of death in the hospital'.*
*- 'Comprehensive Hospital Medicine: An Evidence based approach (Elsevier) 2007/89*

- *Acute Pulmonary Embolism is the third most common cause of hospital death in the united states after heart failure and cancer*
- *Acute Pulmonary Embolism is the most common cause of preventable hospital death*$^{Q}$
- *Acute Pulmonary Embolism is the most common cause of death after surgery in a surgical patient*$^{Q}$

**172. Answer is C (DVT):** *Harrison 17th /1651; 'Peripheral Vascular Disease Basic Diagnostic and Therepeutic Approaches' by Abela (Lippincott Williams) 2004*

***The most common cause of pulmonary thromboembolism is Deep Vein Thrombosis.***

*'A deep vein thrombosis is the most common source of pulmonary embolism' - Peripheral vascular Disease*

***About half the patients with pelvic vein thrombosis or proximal leg deep vein thrombosis have pulmonary thromboembolism. Isolated calf vein thrombosis pose a lower risk of pulmonary embolism*** *– Harrisons*

*'The most common source of pulmonary embolism is deep vein thrombosis of Proximal veins of lower extremity (above knee thrombi). Below the knee thrombi (calf vein thrombosis) by themselves are infrequently associated with embolism unless they extend proximally to the papliteal vein or above' - Peripheral Vascular Disease*

**Remember:**

- **Most common site for deep vein thrombosis:** Calf vein (tendency to embolize is less)
- **Most common *source for pulmonary emboli* :** *Proximal vein of lower extremity* (Pelvic or femoral veins) (tendency to embolize is high)

**173. Answer is C (Large veins of leg):** *Harrison 18th/p 2171 Harrison 15th/ 1509, 16th/ 1561; 17th/ 1651; Bailey and love 24th/866*

***About half the patients with pelvic vein thrombosis or proximal leg deep vein thrombosis have pulmonary thromboembolism. Isolated calf vein thrombosis pose a lower risk of pulmonary embolism*** *– Harrisons*

**174. Answer is D (Progesterone therapy):** *Bailey 23rd/263; CMDT 2002 /233; 2009/260-261*

*"Oestrogen predisposes to thrombosis and not progesterone" - Dutta 4th; Bailey 23rd/263*
*'Pulmonary embolism and deep vein thrombosis are two manifestations of the same disease. The risk factors for pulmonary emboli are the risk factors for thrombus formation.'- CMDT 09/260*

**Inherited disorders predisposing to thrombosis**

| Defective Inhibition of Coagulation Factors | Impaired clot lysis |
|---|---|
| Factors V Leiden resistance (Resistance to activated protein C)<br>Antithrombin III Deficiency<br>Protein C Deficiency<br>Protein S deficiency<br>Prothrombin gene mutation (G40210A)<br>Antiphospholipid antibody or lupus anticoagulant | - Dysfibrogenemia<br>- Plasminogen deficiency$^{Q}$<br>- TPA deficiency<br>- Uncertain Mechanism<br>- Homocystinuria$^{Q}$ |

**Risk factors for vernous throboembolism / Pulmonary thrmoboembolism**

| | |
|---|---|
| Age (Increasing age) $^{Q}$<br>Obesity$^{Q}$<br>Immobility (bed rest > 4 days) $^{Q}$<br>Pregnancy$^{Q}$<br>Puerperium$^{Q}$<br>***High dose oestrogen therapy***$^{Q}$<br>Varicose veins$^{Q}$<br>Inherited disorders as detailed above | Surgery / Trauma$^{Q}$ : Specially of pelvis hip or lower limb<br>Malignancy$^{Q}$: Specially pelvis, abdominal, metastatic<br>Heart failure$^{Q}$ / Recent myocardial infarction<br>Nephrotic syndrome$^{Q}$<br>Inflammatory bowel disease<br>Polycythemia<br>PNH or Lupus anticoagulant$^{Q}$<br>Behcet's syndrome$^{Q}$<br>Homocytinuria$^{Q}$<br>Paralysis of Lower Limnbs<br>Infection |

**175. Answer is C (Sinus Tachycardia ):** *Harrison 18th/p 2172 Harrison 17th/ 1653; Oxford Handbook of Clinical Medicine(OHCM) 5th / 88*

*Sinus tachycardia is the commonest ECG abnormality in pulmonary embolism - OHCM 5th / 88*

**Classic Abnormalities on ECG in pulmonary Embolism**

- Sinus Tachycardia (*Commonest : OHCM*)
- Right ventricular strain pattern (*T wave inversion in leads V1 to V4 perhaps most frequent - Harrison*)
- $S_I Q_{III} T_{III}$ Pattern: (*Classic pattern but rare (OHCM)*)
  - Deeps S waves in lead I
  - Q wave
  - Inverted T wave in lead III
- New onset Atrial Fibrillation / Atrial Flutter.
- Right Axis Deviation / RBBB.

**176. Answer is C (Anticoagulant therapy):** *Harrison 18th/p2172 Harrisons 17th/1653; Clinical Hematology 4th/359*

*D-Dimer values are falsely decreased in patients receiving anticoagulant therapy –Clinical Hematology*
*Myocardial infarction, pneumonia and pregnancy are all established causes for false positive (Elevated) D-Dimer values.*

**D-Dimer**

| Elevated | Decreased |
|---|---|
| True Positive<br>Thromboembolic Diseases<br>• PE • DVT<br>• DIC • Others | Anticoagulant therapy |
| False Positive<br>• MI • Cancer<br>• Pneumonia • Postoperative state<br>• Sepsis • Heart failure<br>• Pregnancy | *The quantitative D-Dimer assay should not be used in patients receiving* anticoagulant therapy *(Warfarin/Heparin) because they will have decreased circulating D-Dimers and can generate a falsely low value* |

**177. Answer is A (Pulmonary Embolism):** *Harrison 18th/p 2172 Harrisons 17th/1653*

***The D-dimer assay is most sensitive for pulmonary embolism with a sensitivity of greater than 95%.***

**Dimmer Assay in P.E (and DVT):**

- D-Dimmer is a specific fragment generated from two cross linked fibrin molecules after a clot has formed
- D-Dimer fragments reach circulation when the fibrin clot is degraded by the action of plasmin (D-Dimer is a fibrin degradation product)
- Elevation of D-Dimer thus indicates that a coagulation fibrinolytic process is taking place.
- Elevation indicates endogenous and often clinically ineffective thrombolysis
- D-Dimer assays are highly sensitive for presence of Thromboembolic Disease
- D-Dimer test is useful as a 'test for exclusion' or a 'rule out test' and is not a diagnostic test.

**D-Dimer Assays**

| Highly sensitive for presence of Thromboembolic Disease | Not specific for presence of Thromboembolic Disease |
|---|---|
| • PE (Sensitivity>95%) | Levels are also increased in |
| • DVT (Sensitivity>80%) | • MI |
| • DIC | • Pneumonia |
| • Other | • Sepsis |
| | • Cancer |
| | • Pregnancy ($2^{nd}/3^{rd}$ trimester) |
| | • Heart failure |
| | • Postoperative state |

**178. Answer is B (Pulmonary Embolism):** *Harrison 18th/p 2172 Harrisons 17th/1653*

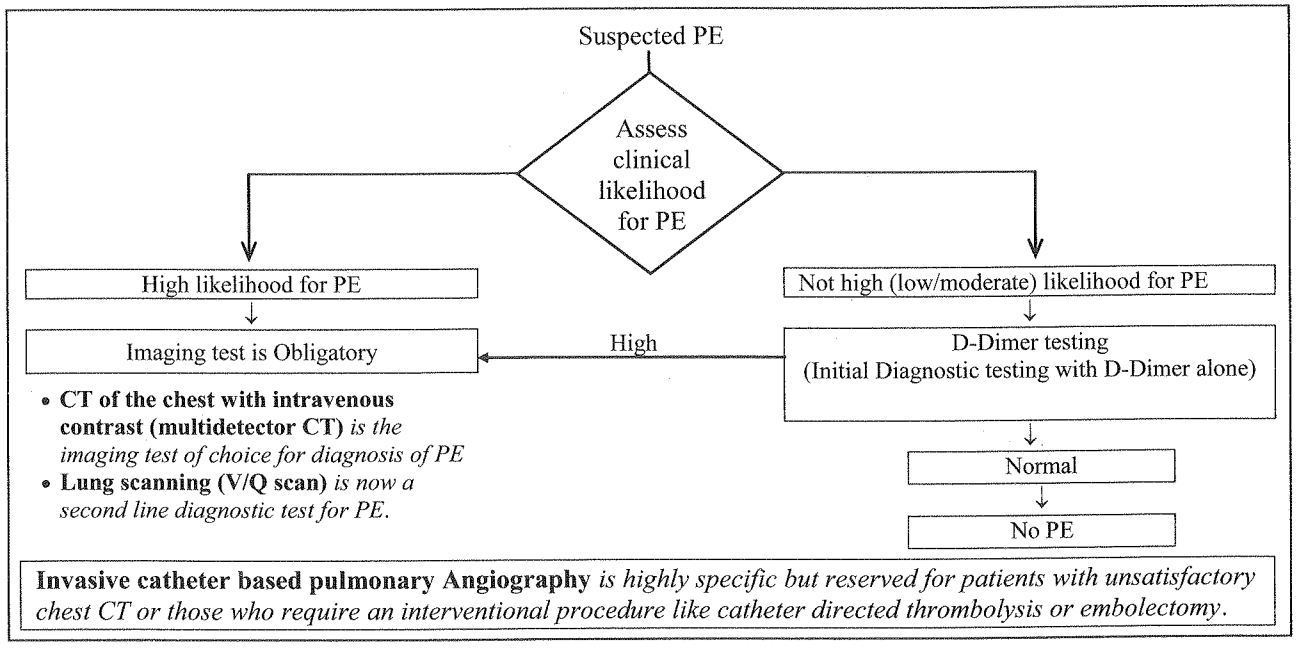
***D-Dimer test is a sensitive test for detection of DVT and PE.***
***Amongst DVT and PE, the D-Dimer test is less sensitive for DVT than PE. (More sensitive for PE)***

*The sensitivity of the D-Dimer assay is greater than 80% for DVT and greater than 95% for PE. The D-Dimer test is less sensitive for DVT than PE because the DVT thrombus size is smaller-Harrison 17th/1653*

**179. Answer is B (Multidetector CT Angiography):** *Harrison 18th/p 2172 Harrison 17th/1652*

***For patients with strong clinical suspicions/high likehood of DVT. Imaging tests are obligatory.***

***CT scan with intravenous contrast (Multidetector CT Angiography) is the test of choice for the diagnosis of PE.***



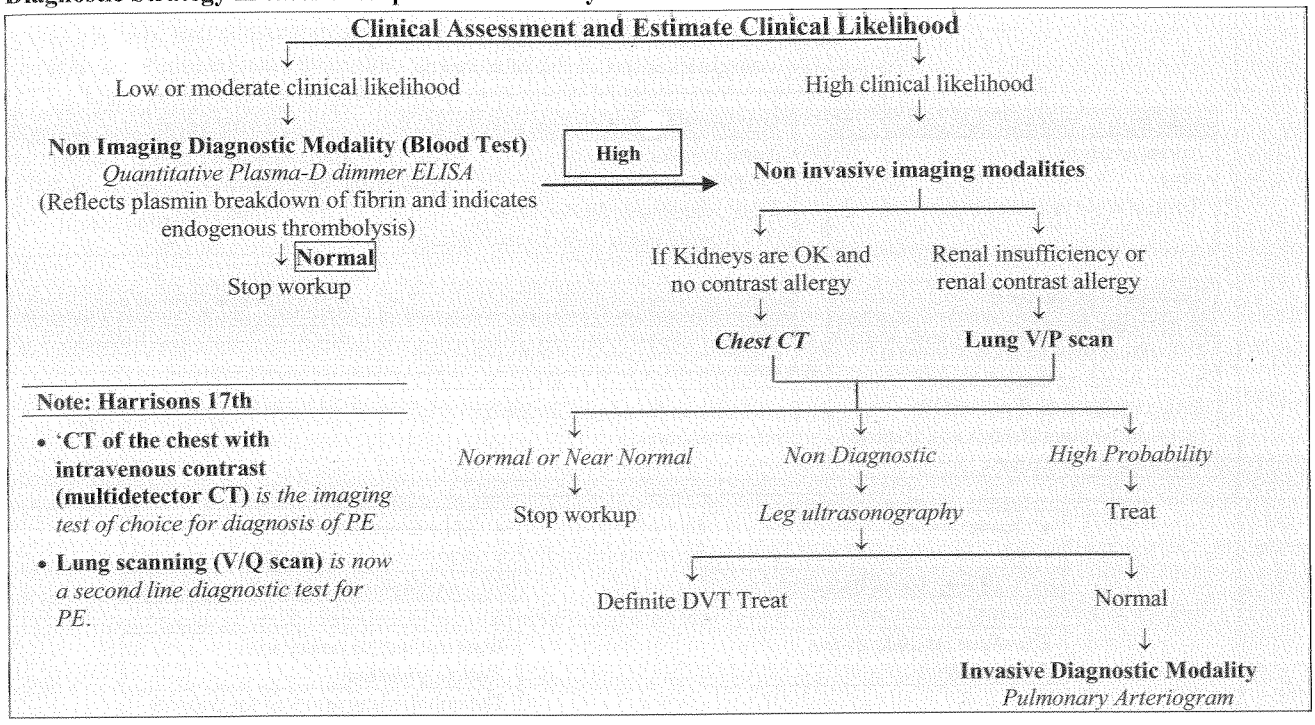
**180. Answer is A (Lung perfusion – ventilation scan):** *Ref: Harrison 15th/ 1510, 1511, 16th/ 1562, 1563; 17th/ 1652, 1663 Harrison 18th/p 2171, 2173*

The clinical picture depicted in the question is suggestive of a ***case of pulmonary thromboembolism.***

*As the patient has a high clinical likelihood, the first investigation should be a non invasive imaging modality in accordance with the diagnostic strategy for PTE outlined in Harrison's textbook.CT of the chest with intravenous contrast (Multidetector CT) is the imaging test of choice but it has not been provided amongst the options.*

***As CT scan of the chest is not provided amongst the options, a Lung Ventilation Perfusion Scan is the modality of choice.***

**Diagnostic Strategy in cases of suspected Pulmonary Thromboembolism**




- *An elderly man on bed rest for past 10 days: predisposition for deep vein thrombosis. (immobilization)*
- *Complaints of breathlessness and chest pain: indicative of pulmonary embolisation. (A chest X-Ray in patient with PTE may well be normal or near normal - Harrison's 15th/1510)*

**Remember:**

*Most specific test for establishing a diagnosis of pulmonary thromboembolism is* ***selective pulmonary angiography***[Q]

**181. Answer is A (Pulmonary arterigraphy):** *Harrison 16th/1563-1564; Harrison 17th/1654 Harrison 18th/p 2173, 2174*

***'Selective pulmonary angiography is the most specific examination available for establishing the definitive diagnosis of PE.'- Harriosn 16th/1563***

**Most definitive investigation** : Pulmonary angiography is an invasive procedure, and it is the most definitive procedure. It is however certainly not the initial investigation of choice.

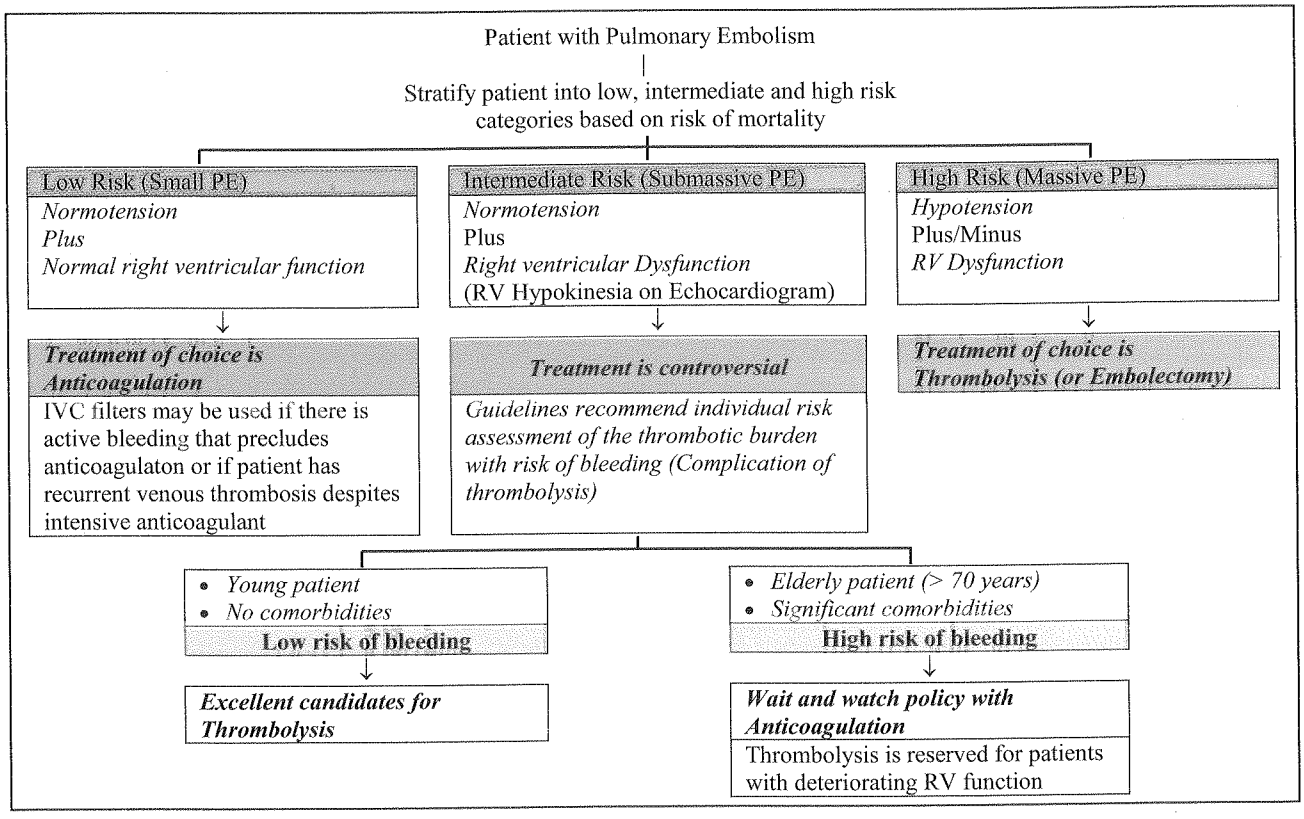
**The initial investigation of choice** in a case of suspected pulmonary embolism is either a lung ventilation perfusion scan or a CT of the chest with intravenous contrast.

*'CT scanning of the chest with intravenous contrast is the principal imaging test for diagnosis of PE.' - Harrison*
*'Lung scanning (V/Q scan) is now a second line diagnostic test for PE'*

| Most definitive / specific test for PE [Q] | Best initial imaging test for diagnosis of PE[Q] |
|---|---|
| *Pulmonary angiography[Q]* | *CT scan with intravenous contrast [Q] (Preferred choice, against a lung V-Q scan)* |

**182. Answer is A (Thrombolytic Therapy):** *Harrison 17th/1654,1655 Harrison 18th/p 2174, 2175*

*Normotension with Right ventricular hypokinesia suggests a diagnosis of submassive pulmonary embolism and stratifies the patient into an intermediate risk category. Treatment for intermediate risk patients with submassive PE is controversial. Guidelines recommend individual risk assessment for the thrombotic burden versus risk of bleeding.* ***According to Harrisons textbook young patients without any comorbidities that fall into the intermediate risk category are excellent candidates for thrombolysis.*** The patient in question is a young 20 years old patient and the question makes no mention of any comorbidities, hence thrombolysis is the single best answer of choice




**183. Answer is A (Thrombolytic Therapy):** *Harrison 18th/ 2174,2175; Guidelines on the diagnosis and management of acute pulmonary embolism: The Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC); (Link: http://eurheartj.oxfordjournals.org/content/29/18/2276.full#sec-40)*

***Thrombolytic therapy is the treatment of choice in patients with High-risk Pulmonary Embolism presenting with cardiogenic shock and/or persistent arterial hypotension.*** *Intravenous unfractionated heparin should be the preferred mode of initial anticoagulation in these patients, as LMWH and fondaparinux have not been tested in the setting of hypotension and shock. Aggressive fluid challenge is not recommended. Experimental studies indicate that aggressive volume expansion may worsen RV function by causing mechanical overstretch and/or by reflex mechanisms that depress contractility.*

| High Risk Pulmonary Embolism (Clinically Massive) | Non-High Risk Pulmonary Embolism | |
|---|---|---|
| | Intermediate Risk (Sub-massive) | Low Risk (Mild) |
| Shock Or Hypotension | Normotension but Right Ventricular Hypokinesis | Normotension and Normal Right Ventricle |
| • ***Anticoagulation*** should be initiated without delay (Intravenous unfractionated heparin should be the | • ***Anticoagulation*** should be initiated without delay (Use of LMWH or fondaparinux is | • ***Anticoagulation*** should be initiated (Use of LMWH or fondaparinux is the |

| | | |
|---|---|---|
| preferred mode of initial anticoagulation in these patients)<br>• ***Thrombolysis*** is the treatment of choice in patients with high-risk PE unless there are absolute contraindications to its use.<br>• ***Surgical embolectomy*** is the preferred therapy in patients with absolute contraindications to thrombolysis and in those in whom thrombolysis has failed to improve haemodynamic status. (If this is not immediately available, ***catheter embolectomy or thrombus fragmentation*** may be considered, though the safety and efficacy of such interventions has not been adequately documented) | the recommended form of initial treatment for most patients)<br><br>• ***Thrombolysis***: Routine use of thrombolysis in non–high-risk PE patients is not recommended, but it may be considered in selected patients with intermediate-risk PE<br><br>Note:<br>Controversy still surrounds the appropriate treatment of this patient group.<br>Therapy needs to be individualized | recommended form of initial treatment for most patients with non-high-risk PE)<br><br>• ***Thrombolytic therapy*** should not be used in patients with low-risk PE<br><br>• ***IVC Filter*** may be considered |

***Note (For High Risk Pulmonary Embolism)***

- *Systemic hypotension should be corrected to prevent progression of RV failure and death due to PE.*
- *Vasopressive drugs are recommended for hypotensive patients with PE.*
- *Aggressive fluid challenge is not recommended*

## Pulmonary Hypertension

**184. Answer is D (≥25mmHg):** *Harrison 18th/ 2079; European Society of Cardiology (ESC) Guidelines for the diagnosis and treatment of pulmonary hypertension*
*(Link: http://www.escardio.org/guidelines-surveys/esc-guidelines/GuidelinesDocuments/guidelines-PH-FT.pdf*

***PH has been defined as an increase in mean pulmonary arterial pressure (PAP) ≥ 25 mmHg at rest as assessed by right heart catheterization (RHC).***

| Definition | Characteristics | Clinical group(s) |
|---|---|---|
| *Pulmonary hypertension (PH)* | • *Mean PAP ≥25 mmHg* | • *All* |
| *Pre-capillary PH* | • *Mean PAP ≥25 mmHg*<br>• *PWP ≤15mmHg*<br>• *CO normal or reduced* | • *Pulmonary arterial hypertension*<br>• *PH due to lung diseases*<br>• *Chronic thromboembolic PH*<br>• *PH with under and/or multifactorial mechanisms* |
| *Post-capillary PH* | • *Mean PAP ≥25 mmHg*<br>• *PWP >15 mmHg*<br>• *CO normal or reduced* | • *PH due to left heart disease* |

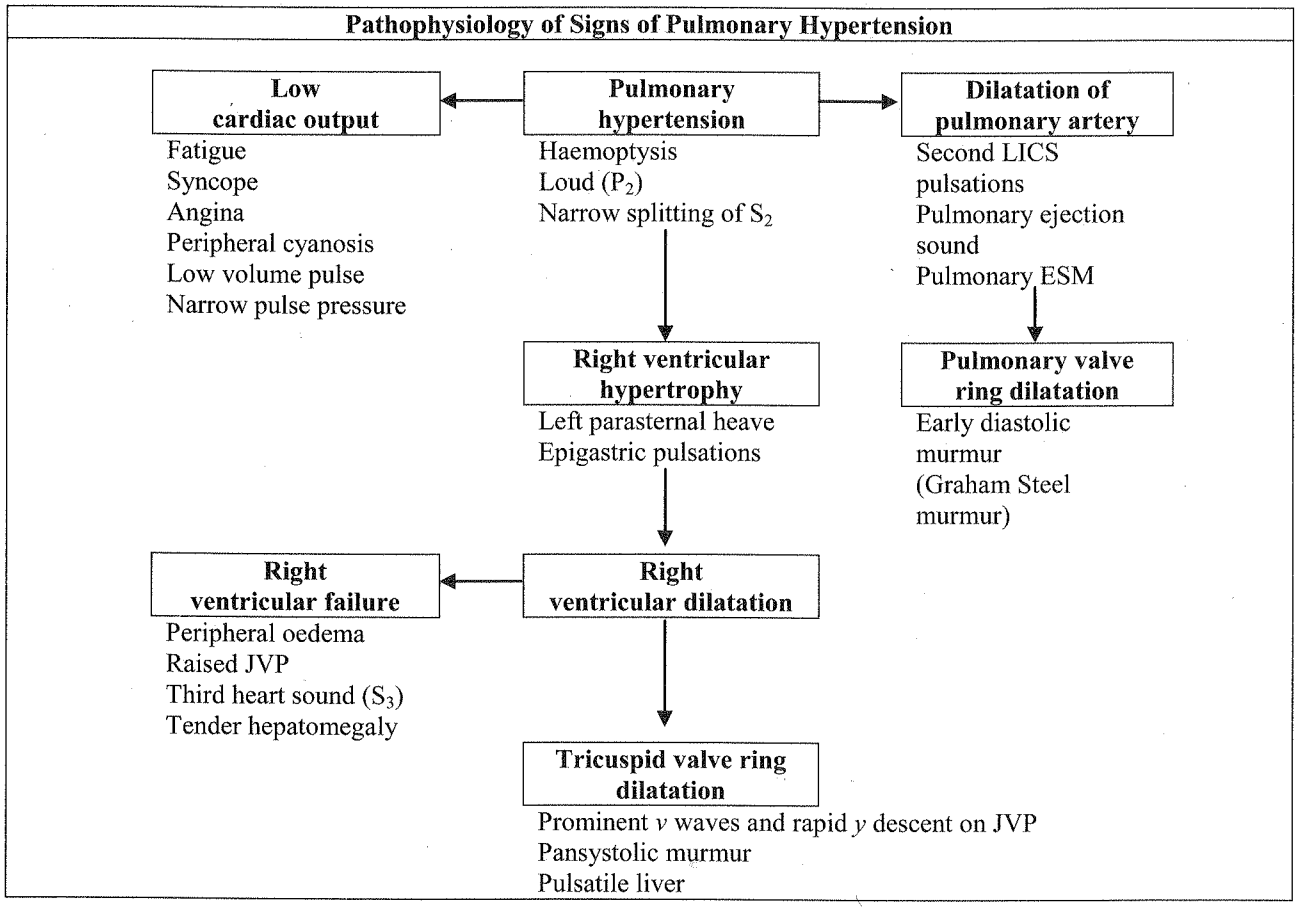
*Note: High CO can be present in cases of hyperkinetic conditions such as systemic to-pulmonary shunts (only in the pulmonary circulation), Anaemia, Hyperthyroidism, etc.*
*CO =cardiac output; PAP =pulmonary arterial pressure; PH = pulmonary hypertension; PWP =pulmonary wedge pressure;*

**185. Answer is B (PAP ≥25mmHg; PCWP ≤15mm Hg):** *Harrison 18th/ 2079; European Society of Cardiology (ESC) Guidelines for the diagnosis and treatment of pulmonary hypertension*
*(Link: http://www.escardio.org/guidelines-surveys/esc-guidelines/GuidelinesDocuments/guidelines-PH-FT.pdf*

***Pre-capillary Pulmonary Hypertension is defined by Mean Pulmonary Artery Pressure (PAP) ≥25mmHg and Pulmonary Capillary Wedge Pressure (PCWP) ≤15mm Hg*** *(thereby excluding a cardiac cause).*

**186. Answer is A (Right Parasternal Heave):** *Medicine: Prep Manual for Undergraduates, 3rd/ 451*

***Pulmonary Hypertension is associated with Right Ventricular Hypertrophy which presents as Left Parasternal Heave*** *(Not Right Parasternal Heave). The Right Ventricle is situated just beneath the left 3rd, 4th, and 5th intercostal spaces close to the sternum and is palpable as a Left Parasternal Heave in cases of Pulmonary Hypertension*

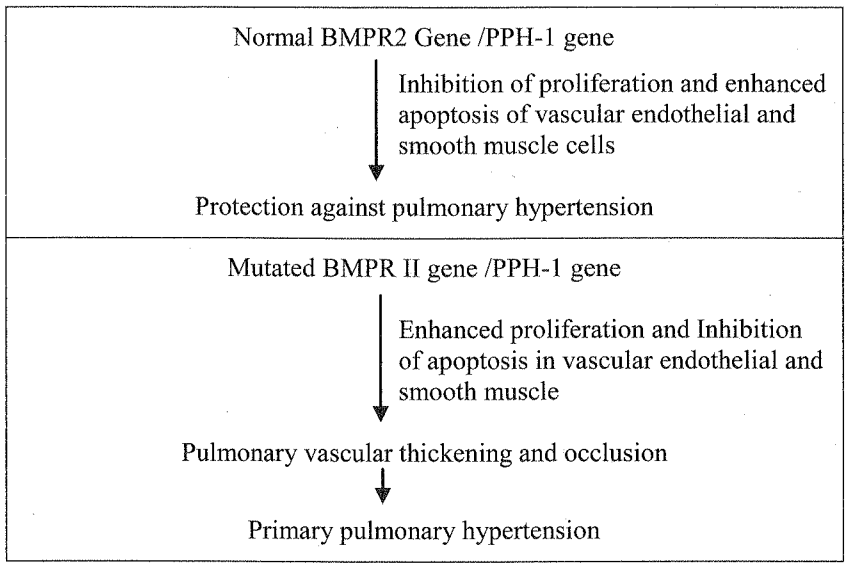



**187. Answer is A (Bone morphogenic Receptor Protein II):** *Harrisons 16th/1405; Harrisons 17th/1577; Robbins 7th /743,744 Harrison 18th/p 2077*

***Gene coding the type II bone morhphogenetic protein receptor II (BMPR II) is associated with familial cases of primary pulmonary hypertension and designated as the PPH I gene.***

Bone morphogenic protein receptor II (BMPRII) and pulmonary Hypertension

- BMPRII is a cell surface protein receptor belonging to the TGF-β receptor superfamily (located on chromosome 2q31)
- BMP-BMPRII signaling plays an important role in embryogenesis, apoptosis, cell proliferation and differentiation.
- In vascular smooth muscles normal BMPR2 signalling causes inhibition of proliferation and favour apoptosis, thereby protecting the vessels from narrowing and development of hypertension
- Primary pulmonary hypertension is believed to be caused by a mutation in the gene coding for the BMPR II signaling pathway (PPH-1 gene/BMPRII gene).
- ***Mutation in the BMPR II gene (PPH-1gene) predisposes the cells to undergo proliferation rather than apoptosis and results in development of pulmonary hypertension.***




**188. Answer is D (↑ Pulmonary wedge pressure):** *Internal Medicine 5th/293*

***↑ pulomary wedge pressure is not a feature of Precapillary Pulmonary hypertension.***

*In precapillary pulmonary hypertension the abnormality that leads to elevated pulmonary pressure is located in the pulmonary artery or arterioles. The Left atrial pressure or Pulmonary capillary wedge pressure is essentially normal.*

| Features | Precapillary | Passive (Post-capillary) |
|---|---|---|
| Pathophysiology | Abnormality that leads to elevated pulmonary artery pressure is located in the pulmoanry artery or arterioles. | Abnormalities that lead to elevated pulmonary artery pressure are located beyond the pulmonary arteries. These are caused by diseases that lead to increased pulmonary venous pressure that in turn produces secondary elevation in pulmonary arterial pressure. |
| Pulmonary artery mean pressure | ↑/↑↑ | ↑ |
| ***Left Atrial Pressure (PCWP)*** | ***Normal*** | ↑ |
| PA left Atrial Pressure Gradient | > 12mm | <12mm Hg |
| Conditions/Causes | • *Primary pulmonary hypertension*<br>• *Disorders of ventilation*<br>• *Congenital heart disease with pulmonary vascular disease*<br>• *Pulmonary embolism*<br>• *Schistosmiasis*<br>• *Collagen vascular disease*<br>• *Pulmonary vasculitis*<br>• *Sickle hemoglobinopathies*<br>• *Portal hypertension*<br>• *Ingestion of drugs and herbal remedies* | • *Left ventricular failure*<br>• *Mitral valve disease*<br>• *Cor triatriatum*<br>• *Obstruction of major pulmonary veins*<br>• *Congenital pulmonary vein stenosis*<br>• *Left atrial myxoma or thrombosis* |

**189. Answer is A (Mitral stenosis):** *Internal Medicine 5th/293*

***Mitral stenosis is a cause of post-capillary pulmonary hypertension or passive pulmonary hypertension.***

**Causes of pulmonary hypertension:**

Precapillary pulmonary hypertension

- ***Primary pulmonary hypertension***
- *Disorders of ventilation*
- *Congenital heart disease with pulmonary vascular disease*
- ***Pulmonary embolism***
- *Schistosmiasis*
- *Collagen vascular disease*
- ***Pulmonary vasculitis***
- *Sickle hemoglobinopathies*
- *Portal hypertension*
- *Ingestion of drugs and herbal remedies*

Passive (Post-capillary) pulmonary hypertension

- *Left ventricular failure*
- ***Mitral valve disease***
- *Cor triatriatum*
- *Obstruction of major pulmonary veins*
- *Congenital pulmonary vein stenosis*
- *Left atrial myxoma or thrombosis*

Reactive pulmonary hypertension

- *Some patients with mitral valve disease*
- *Rarely, other cause of pulmonary venous hypertension, including pulmonary veno-occlusive disease*

**190. Answer is A (Hyperventilation):** *Harrison 18th/p 2078, 2080 Harrisons 17th/1577,1579*

***Pulmonary hypertension may be caused by hypoventilation but not by hyperventilation.***

*Chronic exposure to high altitude sleep disordered breathing due to obesity and anorexic agents including fenfluramine are known causes of pulmonary hypertension.*

Clinical Classification of Pulmonary Hypertension

1. **Pulmonary arterial hypertension (PAH)**
   - Idiopathic (IPAH)(formerly PPH)
   - Familial (FPAH)
   - Associated with (APAH)
     - *Collagen vascular disease*
     - *Congenital systemic-to-pulmonary shunts*
     - *Portal hypertension*
     - *HIV infection*
     - *Drugs and toxins (including fenfluramine)*
     - *Other (thyroid disorders, glycogen storage disease, Gaucher disease, hereditary hemorrhagic telangiectasia, hemoglobinopathies, myeloproliferative, disorders, splenectomy)*
   - Associated with significant venous or capillary involvement
     - *Pulmonary veno-occlusive disease (PVOD)*
     - *Pulmonary capillary hemangiomatosis (PCH)*
     - *Persistent pulmonary hypertension of the newborn*
2. **Pulmonary hypertension with left heart disease**
   - *Left-sided atrial or ventricular heart disease*
   - *Left-sided valvular heart disease*
3. **Pulmonary hypertension associated with lung diseases and/or hypoxemia**
   - *Chronic obstructive pulmonary disease*
   - *Interstitial lung disease*
   - ***Sleep-disordered breathing***
   - *Alveolar hypoventilation disorders*
   - ***Chronic exposure to high altitude***
   - *Developmental abnormalities*
4. **Pulmonary hypertension due to chronic thrombotic and/or embolic disease**
   - *Thromboembolic obstruction of proximal pulmonary arteries*
   - *Thromboembolic obstruction of distal pulmonary arteries*
   - *Nonthrombotic pulmonary embolism (tumor, parasites, foreign material)*
5. **Miscellaneous**
   *Sarcoidosis, histiocytosis X, lymphangiomatosis, compression of pulmonary vessels (adenopathy, tumor, fibrosing mediastinitis)*

*A causal relationship has been established between exposure to several anorexigens including aminorex and the **fenfluramines** and the development of PAH-Harrison*

**191. Answer is D (Argemone mexicana poisoning):** *Harrison 18th/p 2082 Reference with text*

***Argemone mexicana poisoning has not been mentioned as a cause for pulmonary hypertension. It is the single best answer of exclusion.***

**Toxic oil syndrome is associated with pulmonary Hypertension** *(Goldrank's Toxicological Emergencies 7th/25)*
Toxic oil syndrome also called toxic epidemic syndrome is a multi system disorder characterized by pneumonitis, eosinophilia, ***pulmonary hypertension***, scleroderma like feature and neuromuscular changes
Toxic oil syndrome has first observed as an epidemic in spain due to consumption of 'Rapeseed oil' as cooking oil.

**Sickle cell anemia is associated with pulmonary hypertension(H17th/1581)**
*Cardiovascular abnormalities including pulmonary hypertension are prominent abnormalities in the clinical spectrum of sickle cell disease-H17th/1581*

**Systemic sclerosis is associated with pulmonary hypertension**
*All collagen vascular diseases including systemic sclerosis may be associated with pulmonary hypertension.(H17th/1579)*

**192. Answer is D (Bronchoconstriction):** *Harrison 18th/p2081 Harrison 17th/1580*

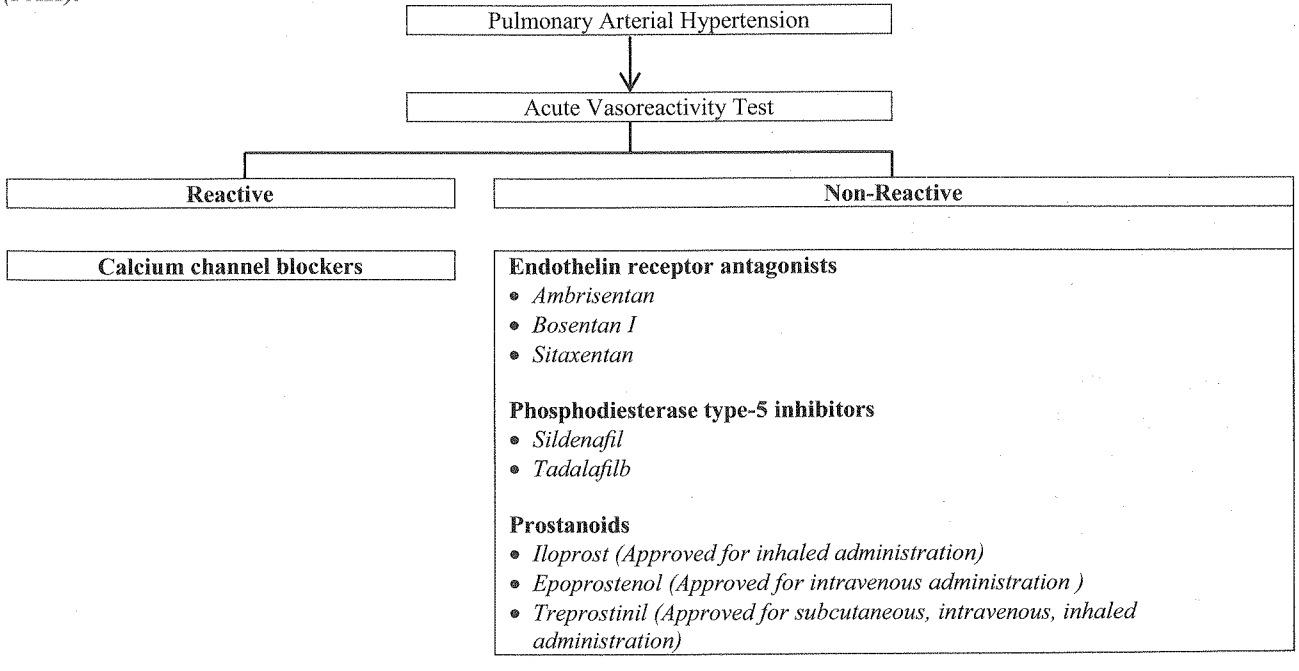
***Bronchoconstriction is not a cause for Pulmonary Hypertension***

**Pulmonary Hypertension in COPD has been attributed to multiple factors including:**

- ***Hypoxia***
- ***Pulmonary vasoconstriction (secondary to hypoxia)***
- *Acidemia*
- *Hypercapnia*
- *Mechanical effect of* ***high lung volume*** *on pulmonary vessels*
- *Loss of small vessels in vascular bed*
- *Regions of emphysematous lung destruction*

**193. Answer is D (Inhalation):** *Harrison 18th/ 2079; European Society of Cardiology (ESC) Guidelines for the diagnosis and treatment of pulmonary hypertension*
*(Link: http://www.escardio.org/guidelines-surveys/esc-guidelines/GuidelinesDocuments/guidelines-PH-FT.pdf*

***Iloprost is a Prostacyclin analogue approved via inhalation for treatment of Pulmonary Arterial Hypertension (PAH).***



**194. Answer is B (Primary Pulmonary Hypertension):** *Harrison 18th/p 2076 Harrisons 17th/1577; Robbins 7th/745; Textbook of Cardiovascular Medicine by Topol 3rd/468; Pulmonary vascular disease 1st (2006)/192*

***Isolated reduction in diffusion capacity (DLCO) with nearly normal flow volumes (FVC; FEV1/FVC) in a young female with progressive dyspnea is characteristic of Primary Pulmonary Hypertension.***

| Features of Primary Pulmonary Hypertension / Idiopathic Pulmonary Arterial Hypertension |
|---|

- *Most common in Young women* who are 20-40 years of Age (Robbin's 7th/745) (strong female predominance)
- *Most common symptom is exertional dyspnea (predominant symptom is dysnea)*
- Pulmonary Function tests
  - *Are usually normal with the exception of DLCO which is characteristically reduced.*
  - *Non obstructive PFT (FEV1/FVC>0.7 or 70%)*
  - *Non restrictive PFT (FVC > 80%)*
  - *DLCO2 is reduced (↓DLCO)*

  (Note: Mild restrictive effects can be seen in upto 20% of patients with advanced IPAH)

| X Ray chest |
|---|

- *X Ray chest shows clear lung fileds in PPH/IPAH*
- *X Ray chest usually shows enlargement of pulmonary arteries*

| Exercise tolerance |
|---|

*Exercise tolerance is markedly reduced*

(The exercise capacity of these patients appears to be limited by a low cardiac output because of a decrease in the functional pulmonary vascular bed)

**Understanding the PFT results of the patient in question**

The patient in question has an almost normal PFT with the exception of a reduced DLCO.

**The patient in question does not have a restrictive disease as FVC >80%**

*Severity of restrictive disease is based on the assessment of FVC.*

| | |
|---|---|
| FVC < 80% | Mild restriction |
| FVC < 70% | Moderate Testriction |
| FVC < 50% | Severe Restriction |

*Patient in question with an FVC of 92% is not a case of restrictive pulmonary disease*

**The patient in question does not have a obstructive lung disease as $FEV_1$/FVC > 0.7 (70%)**

Severity of obstruction is based on FEV1 and FEV/FVC ratio

| | |
|---|---|
| FEV1/FVC ≤ 70; $FEV_1$ ≥80% | Mild obstruction |
| FEV1/FVC ≤ 70; $FEV_1$ ≥ 30% | Moderate obstruction |
| FEV1/FVC ≤70; $FEV_1$ ≤ 30% | Severe obstruction |

*Patients in question has FEV1/FVC > 70% and hence does not have an obstructive lung disease.*

**195. Answer is B (Primary pulmonary hypertension):** *Harrison 17th/1587-1589, 1576, 1576, 1662; 'Spiral manual of pulmonary medicine (Lippincott's)' 6th/444*

***Reduced exercise tolerance and drop in oxygen saturation from 92% to 86% on exercise with a normal FVC and $FEV_1$/FVC is consistent with a diagnosis of Primary Pulmonary Hypertension.***

**Primary Pulmonary Hypertension characteristically presents with exertional dyspnea, exercise intolerance and a normal FVC; FEV1 /FVC ratio**

*The most common symptom attributable to pulmonary hypertension is exertional dyspnea and reduced exercise capacity – Harrison*

*Primary pulmonary hypertension is neither a restrictive nor obstructive pulmonary disease, and hence spirometry results are essentially normal with both FVC and FEV1 / FVC ratio > 80% of predicted.*

| Obstructive disease | Restrictive disease |
|---|---|
| FEV1 / FVC is characteristically < 80% of predicted | FVC is characteristically < 80% of predicted |

**Interstitial lung disease does not present with a normal FVC**

*Interstitial lung disease* should present with a *restrictive pattern on 'pulmonary function tests'* with a *reduced FVC to values less than 80% of predicted.* A forced vital capacity of 90% (FVC = 90%) is normal and hence makes a diagnosis of interstitial lung disease unlikely

**Primary Alveolar Hypoventilation does not present with dyspnea and exercise intolerance**

Patients with primary pulmonary hypoventilation may have normal pulmonary function test with a normal FEV1 and normal FVC/FEV1. However, ***dyspnea or shortness of breath is remarkably absent or extremely uncommon*** despite severe arterial blood gas derangements presumably because of impaired chemoreceptor and ventilatory drive. Also *exacerbation of hypoxemia or* ***drop in oxygen saturation is characteristically seen during sleep*** *and not on exercise.*

*'Despite severe arterial blood gas derangements is uncommon' – Harrison*

*'Dyspnea is remarkably absent' – Spiral Manual of pulmonary Medicine (Lippincott) 6th/444*

**Anxiety disorder: Hyperventilation does not present with exercise intolerance**

Patients with Anxiety associated Hyperventilation may also present with normal spirometry results with a normal FVC and FEV1/FVC. Dyspnea may also be a presenting feature; however such ***patients do not show features of exercise intolerance.***

*'Patients with psychogenic hyperventilation typically complain of dyspnea at rest, but not during mild exercise. During mild or moderate exercise their hyperventilation tends to disappear' - Harrison*

**196. Answer is None or A (None or Pulmonary embolization):** *Harrison 18th/p 1914 Harrisons 17th/1454*

*Recurrent pulmonary embolization leads to chronic cor pulmonale, but the question does not mention 'Recurrent' and hence this is the single best answer of exclusion*

*COPD, Cystic Fibrosis and Bronchiectasis may all progress to chronic cor pulmonale*

**Etiology of Chronic Cor Pulmonale**

| Diseases Leading to Hypoxic Vasoconstriction | Disease That Casue Occlusion of the Pulmonary Vascular Bed | Diseases That Lead to Parenchymal Disease |
|---|---|---|
| ***Chronic bronchitis*** | ***Recurrent pulmonary thromboembolism*** | *Chronic bronchitis* |
| ***Chronic obstructive pulmonary disease*** | ***Primary pulmonary hypertension*** | *Chronic obstructive pulmonary disease* |
| ***Cystic fibrosis*** | *Venocclusive disease* | *Bronchiectasis* |
| *Chronic hypoventilation* | *Collagen vascular disease* | *Cystic fibrosis* |
| *Obsity* | *Drug-induced lung disease* | *Pneumoconiosis* |
| *Neuromuscular disease* | | *Sarcoid* |
| *Chest wall dysfunction* | | *Idiopathic pulmonary fibrosis* |
| *Living at high altitudes* | | |

**197. Answer is B (COPD):** *Rubin's pathology 5th/231*

*The most common cause of chronic cor pulmonale is chronic obstructive pulmonary disease - Rubin's pathology*

Cor Pulmonale

| Acute Cor Pulmonale | Chronic Cor Pulmonale |
|---|---|
| *The most common cause is a sudden, massive, pulmonary embolus* | *The most common cause is COPD* |

**198. Answer is B (Pulmonary thromboembolism):** *Ref: Harrison 15th/ 1355; Harrison 17th/ 1454 Harrison 18th/p 1914*

*Most common causes of acute cor pulmonale is Pulmonary thromboembolism*

***Most common cause of chronic cor pulmonale is Severe COPD.***

**199. Answer is B (Prominent lower lobe vessels) :**

*Chronic Cor Pulmonale is associated with prominence of upper lobe and not lower lobe veins.*

***Features of Congestive Cardiac Failure(CCF / CHF) include :***

1. ***Enlarged cardiac silhouette / Cardiac shadow on chest X-ray*** [Q]
2. Ground glass appearance of pulmonary edema [Q]
3. ***'Kerley B' lines*** [Q]
4. ***Prominence of upper lobe blood vessels*** [Q] *(not lower lobe veins)*
5. *Pleural effusion, usually bilateral* [Q]

- **'*Kerley B' lines*'**, also known as **'*Septal lines*'**, represent dilated lymphatics and distended interlobular septa. They occur ***most commonly in pulmonary edema as a result of chronic pulmonary venous hypertension (in CCF).***
  Kerley 'A' lines stand for Apex, 'B' for Base, and 'C' for Central region.
  ***B lines are most commonly seen*** [Q]. ***Infact they have a relation with left atrial pressure*** [Q] : *They are invariably present if LA pressure goes above 20 mmHg.* [Q]
- Small bilateral ***pleural effusions*** are frequently seen in acute LVF. Large effusion may be present in long standing cases of congestive heart failure.

## Pleural Diseases

### Pleural Effusion

**200. Answer is D (Bronchogenic Carcinoma):** *Harrison 15th/ 1513, 1514; 16th/1567; 17th/ 1660; (table 257.1) Harrison 18th/p 2180 (Table 263.1)*

***Malignant pleural effusions secondary to metastatic disease are exudative in nature. The three tumors that cause approx. 75% of all malignant pleural effusions are lung carcinoma, breast carcinoma, and Lymphoma.***

| **Exudative pleural effusion** | | | **Transudative pleural effusion** |
|---|---|---|---|
| Exudative pleural effusion occurs when ***local factors*** that influence the formation and absorbtion of pleural fluid are altered. | | | Transudative pleural effusion occurs when ***systemic factors*** that influence the formation and absorbtion of pleural fluid are altered. |
| **Distinguishing Laboratory features :** | | | |
| • Total serum protein > 3 gm /dL<br>• *Pleural fluid protein / Serum protein > 0.5*<br>• *Pleural fluid LDH / Serum LDH > 0.6*<br>• *Pleural fluid LDH >2/3 upper limit of serum* | | | Total serum protein < 3 gm /dL<br>*Pleural fluid protein / Serum protein < 0.5*<br>*Pleural fluid LDH / Serum LDH < 0.6*<br>*Pleural fluid LDH<2/3 upper limit of serum* |
| **Causes of Exudative Pleural Effusion:** | | | **Causes of Tansudative Pleural Effusion:** |
| • Neoplastic diseases<br>Metastatic disease<br>Mesothelioma<br>• Infectious diseases<br>Bacterial infections<br>Tuberculosis<br>Fungal infections<br>Tuberculosis<br>Viral infections<br>Parasitic infections<br>• Collagen-vascular diseases<br>Rheumatoid pleuritis<br>SLE<br>Drug-induced lupus<br>Sjogren's syndrome<br>Wegner's granulomatosis<br>Churg-Strauss syndrome | • Gastrointestinal disease<br>Esophageal perforation<br>Pancreatic disease<br>Intraabdominal abscesses<br>Diaphragmatic hernia<br>After abdominal surgery<br>Endoscopy variceal sclerotherapy<br>• After liver transplant<br>• Post-coronary artery bypass surgery<br>• Drug-induced pleural disease<br>Nitrofurantoin<br>Dantrolene<br>Methylsergide<br>Bromocriptine<br>Procarbazine<br>Amiodarone | • Pulmonary embolism<br>• Sarcoidosis<br>• Uremia<br>• Asbestos exposure<br>• Meig's syndrome<br>• Yellow nail syndrome<br>• Trapped lung<br>• Radiation therapy<br>• Post-cardiac injury syndrome<br>• Hemothorax<br>• Iatrogenic injury<br>• Ovarian hyperstimulation syndrome<br>• Pericardial disease<br>• Chylothorax | 1. Congestive heart failure<br>2. Cirrhosis<br>3. Pulmonary embolization<br>4. Hephrotic syndrome<br>5. Peritoneal dialysis<br>6. Superior vena cava obstruction<br>7. Myxedema<br>8. Urinothorax |

**201. Answer is D (Pleural fluid ADA and Serum ADA <16):** *Harrison 18th/ 2178*

***Ratio of Pleural fluid ADA and Serum ADA <16 is not part of Light's Criteria.***

***Light's criteria**, rely on a comparison of the chemistries in the pleural fluid to those in the blood, to establish the cause of the effusion as transudate or exudates.*

| **According to Light's criteria a pleural effusion is likely exudative if at least one of the following exists** |
|---|
| • *The ratio of pleural fluid protein to serum protein is greater than 0.5* |
| • *The ratio of pleural fluid LDH and serum LDH is greater than 0.6* |
| • *Pleural fluid LDH is greater than 0.6 or 2/3 times the normal upper limit for serum.* |

*Note:*

*Exudative Pleural Effusions meet at least one of the above criteria while transudative effusions meet None*
*These criteria misidentify around 25 percent of transudates as exudates*

**202. Answer is A (Proteins<3gm) :** *Textbook of Pulmonary Medicine By D. Behera 2nd/1564; Clinical Hematology: Theory and Procedures By Mary Louise Turgeon 4th/ 461*

***Proteins less than 3 gm is suggestive of a Trasudate.***

| **Comparison of Transudates and Exudates** | | |
|---|---|---|
| **Characteristics** | **Transudate** | **Exudate** |
| | *Increased hydrostatic pressure. Decreased colloid osmotic pressure* | *Increased Vascular Permeability Inflammation;Infection* |
| Physical Characteristics | | |
| Appearance | Clear | Cloudy, Turbid |
| pH | 7.4-7.5 | 7.35-7.45 |
| Specific gravity | <1.016 | >1.016 |
| Cellular Characteristics | | |
| Erythrocytes | few | variable |
| Leukocytes | < 1,000<br>Typically <250 /$mm^3$<br>Few Neutrophils<br>Few Lymphocytes | >1,000<br>Typically >1000/$mm^3$<br>Predominance of Neutrophils suggests infection and an exudative effusion.Predominance of Lymphocytes may suggest Tuberculosis |
| Chemical Analyses | | |
| Glucose level | Equal to serum levels | Possibly decreased |
| Protein level | <3.0g/dl | >3.0g/dl |
| Pleural fluid-serum Ratio of protein | <0.5 | >0.5 |
| LDH level | Low (< 200) | High (>200 IU/L) |
| Pleural fluid- serum Ratio of LDH | <2:3 (<0.6) | >2:3 (>0.6) |
| Pleural fluid cholesterol | <55mg/dl | >55mg/dl |
| Serum: Pleural albumin gradient | <1.2 mg/dl | >1.2 mg/dl |
| Fluid; serum bilirubin | <0.6 | =/>0.6 |

**203. Answer is A (Serum Pleural Albumin ratio <1.2mg/dl):** *Textbook of Pulmonary Medicine By D. Behera 2nd/1564*

***Exudative effusions are typically associated with Serum Albumin : Pleural Albumin ratio > 1.2mg/dl.***

Biochemical Differentiation between transudative and exudative effusion:

| Character | Exudates | Transudates |
|---|---|---|
| Pleural fluid LDH level | >200 or > 2/3rd of serum | < 200 or < 2/3rd of serum |
| ***Fluid; Serum LDH*** | ***>0.6*** | ***<0.6*** |
| ***Fluid; serum protein*** | ***>0.5*** | ***<0.5*** |
| Pleural fluid cholesterol | >55mg/dl | <55mg/dl |
| Serum pleural albumin gradient | >1.2 mg/dl | <1.2 mg/dl |
| Fluid; serum bilirubin | =/>0.6 | <0.6 |

**204. Answer is B (Rheumatoid arthritis):** *Harrison 18th/p 2178, 2179, 2180 Harrisons 17th/1658, 1659, 1660 (±)*

***Rheumatoid Arthritis is a cause for exudative pleural effusion***

**205. Answer is A and E (Pancreatitis and Esophageal rupture):** *Kundu 3rd/ 52*

***Predominantly left side effusion is a feature of Pancreatic effusion and effusion secondary to esophageal rupture.***

**Pleural Effusion**

| Predominant left sided pleural effusion | Predominant right sided pleural effusion |
|---|---|
| • *Acute pancreatitis* | • *Amoebic liver abscess* |
| • *Oesophageal rupture* | • *Cirhosis of liver* |
| • *Dressler's syndrome (postmyocardial infarction syndrome)* | • *Congestive cardiac failure* |
| | • *Meig's syndrome (fibroma of ovary with ascites ad pleural effusion)* |

**206. Answer is A and E (Horizontal fluid level and succussion splash):** *Refer text below*

***Succussion splash & horizontal fluid levels are features of hydropneumothorax & not pleural effusion.***
***Pleural efusions are associated with decreased chest movements, decreased lung volumes and may be associated with diminished heart sounds***
***Fluid level is typically concave & succession splash is not demonstable***

**Succussion splash is a feature of Hydropneumothorax and not pleural Effusion**

Fluid movement in a cavity devoid of air is silent. When the cavity contains both air and fluid, body movements cause a splash audible to the patient and examiner – *succussion splash*

- A succussion splash in the thorax suggests a hydropneumothorax
- A succussion splash in the thorax may also result from a fluid filled stomach herniating into the thorax through a diaphragmatic hernia
- A succussion splash in the thorax in theory might be produced by a lung abscess, but in practice this almost never occurs because the pus is so thick that it does not splash.

**Horizontal Fluid level is a feature of Hydropneumothorax**

*Pleural effusion presents with a concave fluid level (concave upper edge)*
*Presence of horizontal fluid level indicates the presence of associated air in the pleural cavity and suggests a diagnosis of Hydropneumthorax.*

**207. Answer is D (Increased Mesothelial cells):** *Harrison 14th/ 1474; 15th/ 1514; 16th/1567; 17th/ 1658, 1659 Harrison 18th/p 2178, 2179*

***Presence of Mesothelial cells > 5% make diagnosis of Tubercular effusion unlikely*** *– CMDT 2009/277 t 9-23*

**Characteristics of Tuberculous effusion**

- Exudative
- Proteins increased (Pleural fluid protein / Serum protein > 0.5)
- Pleural fluid LDH increased (P. Fluid LDH/ Serum LDH > 0.6
- Haemorrhagic
- Glucose: equal to serum levels; occasionally < 60 mg/dl
- WBC count increased: predominantly small lymphocytes
- High levels of TB markers in pleural fluid
  - Adenosine deominase > 45 IU/L
  - Interferon V > 140 pg/ml
  - Positive PCR for tubercular DNA

*Eosinophils > 10% or mesothelial cells > 5% make diagnosis of tubercular effusion unlikely.*

**208. Answer is None > A (None > Tuberculosis):** *Harrison 18th/p 2179 Harrisons 17th/1658; Fishman's textbook of pulmonary Diseases and Disorder's 4th/1488; CMDT 2008/269; 2009/277 t 9-23*

***Parapneumonic effusions (bacterial infections), Rheumatoid effusions, Malignant effusions (Mesothelioma) and Tuberculous effusions are all established causes that may present with low glucose (<60 mg/dl) in pleural fluid.*** *Although tuberculosis may present with low glucose levels and is included in the differential diagnosis for conditions with low glucose in pleural fluid, the glucose levels in Tuberculosis is more often equal to serum levels. Tuberculosis is therefore the single best answer of exclusion amongst the options provided.*

| *Glucose levels in TB are usually equal to serum levels but Tuberculosis may present occasionally with Glucose < 60mg/dl- CMDT 09/277* |
|---|

**According to Fishman's textbook** on pulmonary disease, the presence of pleural fluid glucose below 60 mg/dl narrows the diagnostic possibilities to seven conditions.

| Conditions associated with Decreased Glucose (<60mg/dl) in pleural fluid |
|---|
| • *Malignant Effusion*[Q] *(Also mentioned in Harrisons)* |
| • *Rheumatoid Effusion*[Q] *(Also mentioned in Harrisons)* |
| • *Parapneumonic Effusion*[Q] *(Bacterial Infections as mentioned in Harrisons)* |
| • *Tuberculous Effusion*[Q] *(Also mentioned in CMDT)* |
| • *Hemothorax* |
| • *Paragonimiasis* |
| • *Churg-Strauss Syndrome* |

**209. Answer is D (Dressler's Syndrome):** *Harrison 18th/p 2178 Harrisons 17th/1658; Fishman's Pulmonary Diseases and Disorders 4th/1488*

***Dressler's Syndrome is not associated with low glucose in pleural fluid.***
***Rheumatoid Arthritis, Malignancy and Empyema (Bacterial infections) are all established causes of pleural effusion with low glucose.***

| Pleural effusion with low glucose (< 60 mg/dl) |
|---|
| 1. Malignancy |
| 2. Bacterial infections |
| 3. Rheumatoid pleuritis |

**210. Answer is A (Dressler syndrome):** *Harrison 18th/p 2178 Harrison 15th/ 1513; Harrison 16th/ 1566; Harrison 17th/ 1658 (Fig. 257.1)*
***Dressler's Syndrome is not associated with low glucose in pleural fluid.***
***Rheumatoid Arthritis, Malignancy and Empyema (Bacterial infections) are all established causes of pleural effusion with low glucose.***

**211. Answer *is A and C (Rheumatoid arthritis and Pneumococcal infection)*** *Refer Previous question*

***Rheumatoid Effusion and effusion secondary to bacterial infections (pneumococcus) are established causes for decreased glucose in pleural fluid.***

**212. Answer is B (Malignancy):** *Harrison 17th/ 1658; (Fig. 257.1); CMDT 2009/ 276 Harrison 18th/p 2178*

***Malignancy is associated with high levels of amylase in pleural fluid***

| High amylase level in pleural fluid suggests |
|---|
| Esophageal rupture[Q] |
| Pancreatic pleural effusion[Q] (Pancreatitis/Pancreaticpseudo cyst) |
| Malignancy[Q] (Adenocarcinoma of lung/pancreas) |

**213. Answer is A (Rheumatoid arthritis):** *Refer previous question*

***Rheumatoid Arthritis is not associated with increased amylase in pleural fluid.***

| Conditions with High Amylase in pleural Fluid |
|---|
| • *Esophageal Rupture* [Q] |
| • *Pancreatic effusion* [Q] |
| • *Malignancy* [Q] |

**214. Answer is A (Myxoedema):** *See text below*

***Pleural effusion secondary to Myxoedema (Hypothyroidism) is associated with presence of cholesterol crystals.***

| Pleural effusion with cholesterol crystals |
|---|
| • *Hypothyroidism (myxoedema)* |
| • *T.B.* |
| • *Rheumatoid arthritis* |

**215. Answer is B (7th Intercostal space in mid axillary line):** *Pretest Anatomy; P.J. Mehta 13th/361*

***Site of pleural effusion drainage is seventh intercostal space in mid-axillary line.***

## Pneumothorax

**216. Answer is D (Bronchopulmonary Aspergillosis)**

***Bronchopulmonary Aspergillosis has not been mentioned as a cause for penumothorax.***
*Artificial ventilation is an established cause for iatrogenic pneumothorax while Marfan's syndrome and Eosinophilic granuloma are established causes for secondary spontaneous pneumothorax.*

Pneumothorax

**Spontaneous Pneumothorax**

**Primary Spontaneous Pneumothorax**
- Occur in persons with No clinical evidence of lung disease and without precipitating event
- Most of these patients have occult lung disease (sub clinical) with subpleural blebs on CT scan

Characteristics of affected people are
- *Tall, thin, males♀*
- *Smokers♀*
- *Subpleural blebs♀ on lungs*

**Secondary spontaneous pneumothorax**
- Occurs in persons with an underlying lung disease as a complication of the underlying disease process

**Etiology of Secondary Pneumothorax**

| Obstructive Lung Disease |
|---|
| *Chronic obstructive lung disease (COPD)* |
| *Asthma* |
| **Interstitial lung disease** |
| *Idiopathic pulmonary fibrosis (usual interstitial pneumonitis (UIP))* |
| *Non-specific interstitial pneumonitis* |
| ***Eosinophillic granuloma*** |
| *Lymphangioleimyomatosis* |
| *Sarcoidosis* |
| *Langerhans cell granulomatosis* |
| *Radiation pneumonitis of fibrosis* |
| *Histocytosis X* |
| **Infection** |
| *P. jerovici pneumonia* |
| *Tuberculosis* |
| *Coccidioodomycosis* |
| *Acute bacterial pneumonia (i.e. staphylococcus)* |

| Malignancy |
|---|
| *Primary lung carcinoma* |
| *Pulmonary metastasis (especially sarcomas)* |
| *Complications of chemotherapy* |
| **Connective tissue disease** |
| *Rheumatoid arthritis* |
| *Ankylosing spondylitis* |
| ***Marfan's syndrome*** |
| *Ehlers-Danlos syndrome* |
| *Polymyositis/dermatomyositis* |
| *Scleroderma* |
| **Other** |
| *Catamenial pneumothorax* |
| *Pulmonary infarction* |
| *Pulmonary hemorrhage* |
| *Pulmonary alveolar proteinosis* |
| *Tuberous sclerosis* |
| *Von Recklinghausen's disease* |
| *Wegner's granulomatosis* |

**Traumatic Pneumothorax**
(Non spontaneous Pneumothorax)
- These penumothoroces occur as a result of:
  - Blunt trauma or
  - Penetrating trauma
- Iatrogenic penumotharax is subcategory of Traumatic Pneumothorax

Causes of Iatrogenic Pneumothorax
- Thoracocentesis
- Insertion of central venous catheter
- ***Mechanical ventilation*** (IPPV, Assisted ventilation etc)
- Surgery

**217. Answer is B (Pneumothorax):** *Handbook Of Critical Care By Paul Ellis Marik / 469*

***Pneumothorax and/or less commonly hemothorax occurs due to injury to pleura and underlying Lung***
*– Critical care handbook.*

**218. Answer is B (Old age):** *Harrison 18th/p 2181 Harrisons 17th/1660; CMDT 2008/271; 2009/278*

***Primary spontaneous pneumothorax is characteristically affects young individuals and not elderly individuals.***

Primary Spontaneous Pneumothorax (Primary pneumothorax)

- ***Primary spontaneous penumothorax occurs in persons with no clinical evidence of lung disease and often without an obvious precipitating event***
- Most of these patients have occult lung disease (sub clinical lung disease) in the form of subpleural apical blebs (recognized on CT scan)
- *Characteristic risk factors include a positive family history and history of smoking (occurs almost exclusively in smokers according to Harrisons)*
- *Characteristically affects tall, thin boys and men between the age of 10 and 30 years*

**Primary Spontancous pneumothorax**
- *No clinical evidence of pre existing lung disease*[Q]
- *Rupture of apical subpleural blebs*[Q]
- *Positive family history*[Q]
- *History of smoking*[Q]
- *Tall and thin individual* [Q]
- *Young adults (10 to 30 years of age)* [Q]
- *Male gender*[Q]

**219. Answer is A (smokers):** *Repeat*

***Spontaneous pneumothorax is common in smokers.***

*Spontaneous pneumothorax characteristically affect young, tall and thin men/boys (male gender).*

**220. Answer is A (Decreased Chest Expansion):** Refer Text Below

***Chest Expansion may be Normal or Decreased in Pneumothorax.***
*Pneumothorax is associated with reduced breath sounds, reduced vocal resonance, hyper-resonant percussion note and tracheal deviation/mediastinal shift to opposite side.*

| | Tracheal deviation (Mediastinal shift) | Chest expansion | Percussion note ↓ Duller ↑ Hyper-resonant | Breath sounds ↑ Louder ↓ Softer | Added sounds | Vocal resonance |
|---|---|---|---|---|---|---|
| **Consolidation** | No | Normal, or↓ | Normal, or↓ | ↑ (Bronchial) | Coarse crackles +/- rub | ↑ Whispering Pectoriloquy |
| **Lobar collapse** | Yes (Towards collapse) | ↓ | ↓ | ↓ | No | ↓ |
| **Pleural effusion** | No | ↓ | ↓ (Stony dull) | ↓ | Occasional rub | ↓ |
| **Pneumothorax** | Yes (Specially with tension) | Normal or↓ | ↑ | ↓ | Occasional click | ↓ |

**221. Answer is D (Often need chest tube insertion):** *CMDT 2008/272; 2009/279*

***Pneumothorax is associated with decreased breath sounds, hyperresonant (increased) percussion note. Chest tube drainage is often required but is not necessary in all cases.***

*Many small pneumothoraces resolve spontaneously as air is reabsorbed from the pleural space. In reliable patients with small stable pneumothorax observation alone may be appropriate*

**222. Answer is A (Needle puncture and emergent decompression):** *Harrison 18th/ 2181*

*Sudden Onset Respiratory Distress (which is increasing) and a Hyper-resonant percussion note in a patient with history of chest trauma suggest a diagnosis of Tension Pneumothorax.* ***Needle puncture and emergent decompression is the treatment of choice for Tension Pneumothorax***

***Tension pneumothorax must be treated as a medical emergency and therapeutic intervention should not be delayed while waiting for investigations. Immediate puncture of pleura with a large bore needle through the second intercostal space is the treatment of choice.***

**223. Answer is D (Large Bore needle puncture of pleura):** *Harrison 18th/p 2181 Harrisons 17th/1660*

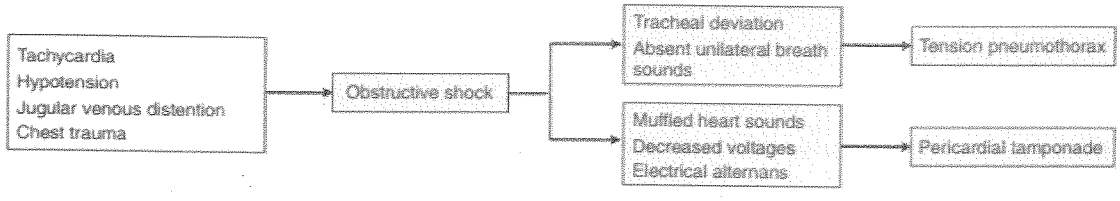
*Acute breathlessness absent breath sounds, neck vein distension and mediastinal shift suggests a diagnosis of Tension Pneumothorax.*

***Tension pneumothorax must be treated as a medical emergency and therapeutic intervention should not be delayed while waiting for investigations. Immediate puncture of pleura with a large bore needle through the second intercostal space is the treatment of choice.***

**224. Answer is D (Tension Pneumothorax):** *ATLS Guidelines; Refer text below*

***Presence of Severe Respiratory Distress in a patient with Hypotension and Tachycardia suggests a diagnosis of Tension Pneumothorax.***

Hypotension, Tachycardia and Shortness of breath may be seen in Massive Hemothorax, Cardiac Tamponade and Tension Pneumothorax. Differentiation of these conditions requires further clues in the form of tracheal deviation (Deviated in Pneumothorax), percussion note (Dull in Hemothorax), Jugular Venous Pulse (Normal in Hemothorax), Heart Sounds (Muffled in Cardiac Tamponade). In the absence of such clues, presence of severe respiratory distress favours a diagnosis of Tension Pneumothorax.




**225. Answer is B (Massive Hemothorax):** *Refer Text Below: ATLS Guidelines*

***Features of Shock in a patient with Chest- Trauma without an elevated JVP suggest a diagnosis of Massive Hemothorax.***

| | Tension Pneumothorax | Cardiac Tamponade | Massive Hemothorax | Simple Pneumothorax |
|---|---|---|---|---|
| Presenting Feature | Respiratory Distress (Shock may be the presenting feature but less common) | Shock (Shortness of Breath may be seen) | Shock (Shortness of Breath may be seen) | Shortness of breath may be seen<br>No Shock (No Hypotension or Tachycardia) |
| Neck Veins | Distended | Distended | ***Not Distended*** | Not distended |
| Trachea | Deviated | Midline | Midline | Usually Midline |
| Breath Sounds | Decreased or absent on side of injury | Normal | Decreased or absent on side of injury | May be decreased on side of injury |
| Percussion Note | Hyper-resonant | Normal | Dull | May be Hyper-resonant |
| Heart Sound | Normal | Muffled | Normal | Normal |

**226. Answer is A (Left axis deviation):** *Repeat*

***Left-sided pneumothorax is associated with right axis deviation.***

**227. Answer is B (Pleural effusion):** *Harrison 14th/ 1489, 15th/ 1530; Harrison 17th/ 1688 Harrison 18th/p 2213, 2215*

***Pleural effusion has not been mentioned as a complication of IPPV.***

**Complications of endotracheal intubation and positive pressure mechanical ventilation include :**

| Pulmonary complications: | Gastrointestinal complications: | Others: |
|---|---|---|
| 1. ***Barotrauma*** | 1. *Stress ulceration* Q | 1. Malnutrition |
| 2. Nosocomial pneumonia | 2. Mild to moderate *cholestasis* Q | 2. *Decubitus ulcers* Q |
| 3. *Oxygen toxicity* Q | | 3. *Venous thrombosis* Q |
| 4. *Tracheal stenosis* Q | | 4. *Depression* Q |
| 5. Deconditioning of respiratory muscles | | |

## Disorders of Ventilation and Mediastinitis

**228. Answer is D (10 seconds):** *Harrison 18th/p2186, 2187 Harrisons 17th/1665,1666; Harrisons 16th/1573,1574; CMDT 2008/273; 2009/280*

***Sleep Apnea is defined as temporary cessation of breathing for at least 10 seconds (CMDT)***

**Sleep Apnea:** Review

- Sleep Apnea is defined as an intermittent cessation of airflow at the nose and mouth during sleep
- ***By definition/convention breath cessation for at least 10 seconds is termed Apnea***

> *By convention sleep apnea is defined by breath cessation for at least 10 seconds. Most patients with sleep apneas have cessation for 20-30 seconds. The duration of breath cessation may be as long as 2-3 minutes.*

- Sleep apneas can be central or obstructive

| Central sleep Apnea | Obstructive sleep Apnea |
|---|---|
| Sleep apnea occurs due to transient cessation of neural drive to all respiratory muscles | Sleep Apnea occurs due to transient occlusion of the orapharyngeal airway despite continued respiratory drive |

**229. Answer is A (> 10 seconds):** Companion to Clinical Neurology 2ND/869; *CMDT 2014/ 318*

***Duration of apnea episodes in obstructive sleep apnea syndrome is typically less than 10 seconds.***

Obstructive Sleep Apnea Syndrome is defined as the coexistence of unexplained daytime sleepiness with more than five obstructive apneic episodes, greater than 10 seconds in duration, per hour of sleep

**230. Answer is C (Sleep Apnea):** *Harrison's 18th / 2184; Primary Care Tools for Clinicians: A Compendium of Forms and Questionnaires*

***Epworth scale is used for assessing Obstructive Sleep apnea.***

*Epworth scale also known as The Epworth sleepiness scale (ESS) is a quantitative subjective tool to measure 'sleepiness' and is often used to evaluate measure of how sleepiness interferes with an individual's common daily activities. The Epworth Sleepiness Scale is the most frequently used self-administered questionnaire to evaluate daytime sleepiness and has been used for the evaluation of several sleep disorders.*

| The Epworth Sleepiness Scale (Common Indications) |
|---|
| • *Obstructive sleep apnea* |
| • *Narcolepsy* |
| • *Idiopathic hypersomnia* |

**231. Answer is A (Does not respond to chemical stimuli):** *Harrison 18th/p 2183; 15th/ 1518; 16th/1570; 17th/ 1663*

***Ventilatory responses to chemical stimuli are reduced or absent*** *– Harrison 16th/1570*

**Primary pulmonary hypoventilation**

| **Characterized by:** |
|---|
| *Impaired chemoreception resulting in decreased ventilatory drive.*<br>Chronic hypercapnia and hypoxemia in the absence of identifiable neuromuscular disease or mechanical ventilatory impairment. |
| **Presentation :** |
| Occurs in all age groups but majority of cases have been reported in males aged 20-50 years.<br>Early: lethargy, fagtigue, daytime somnolence, disturbed sleep and morning headache.<br>Late: Cyanosis polycythemia, pulmonary hypertension, congestive heart failure.<br>Note : Dyspnea is uncommon despite severe arterial blood gas derangements because of impaired chemotherapy. |
| **Diagnosis :** |
| The key diagnostic feature is respiratory acidosis in the absence of respiratory muscle weaknesses or impaired ventilatory mechanics. |

**232. Answer is B (Causes normocapnic failure):** *Harrisons 15th/1516; Harrison 16th/1569; Harrison 17th/221, 1663*

***"Most patients with severe diaphragmatic weakness present with hypercapnic respiratory failure"*** *-Harrison*

- **Sniff test** is a confirmatory test of ***unilateral diaphragmatic paralysis***. *Whether sniff test is also useful for bilateral diaphragmatic paralysis is unconfirmed,* although it could show a paradoxical diaphragm movement on both sides. (The person is asked to sniff and is observed with fluoroscopy. The paralyzed diaphragm moves paradoxically upwards during inhalation due to negative intrathoracic pressure.)
- **Diaphragmatic pacing** may be a viable alternative if the nerve to the diaphragm is intact.
  Treatment of choice for Bilateral Diaphragmatic Paralysis is assisted ventilation

**Note:**

1. Unilateral paralysis occurs due to more local cause e.g. nerve invasion from bronchogenic carcinoma. Patients are usually asymptomatic.
2. Bilateral paralysis occurs due to more central or generalized causes e.g. high spinal cord injury, muscular dystrophy chest trauma.
   Patients present with hypercapnic respiratory failure, frequently complicated by cor-pulmonale, right ventricular failure (because of hypoxemic vasoconstriction in the lungs) pneumonia and atelectasis.

**233. Answer is B (Esophageal rupture):** *Ref: Harrison 14th/ 1475; 15th/ 1516; 16th/1568; 17th/ 1660, 1661; 18th/p 2182*

***Most cases of acute mediastinitis are due to esophageal perforation or occur after median sternotomy for cardiac surgery*** *– Harrison*

| Acute Mediastinitis | Chronic Mediastinitis |
|---|---|
| 1. Esophageal rupture $^{Q}$ | 1. Tuberculosis / Histoplasmosis (most cases) $^{Q}$ |
| 2. Median sternotomy for cardiac surgery | 2. Sarcoidosis, silicosis $^{Q}$ |
| | 3. Other fungal diseases |

## Bronchogenic carcinoma

**234. Answer is D (Adenocarcinoma):** *Ref: Harrison 15th/ 562; Harrison 16th/ 506; Harrison 17th/ 552 Harrison 18th/p 738*

***Most common Bronchogenic Ca in world is Adenocarcinoma***

***Most common Bronchogenic Ca in India is Squamous ca***

| Histological type | Frequency |
|---|---|
| Adenocarcinoma | 32% |
| Squamous cell ca | 29% |
| Small cell carcinoma | 18% |
| Large cell carcinoma | 9% |
| Carcinoid | 1% |

**Facts to remember**

| | |
|---|---|
| ϱ *Most frequent histological type* | *: Adenocarcinoma* |
| ϱ *Most frequent histological type in India* | *: Squamous cell carcinoma* |
| ϱ *Most common histological variety in life time non-smokers* | *: Adenocarcinoma* |
| ϱ *Most common histological variety in young patients.* | *: Adenocarcinoma* |
| ϱ *Most common histological variety in females* | *: Adenocarcinoma* |
| ϱ *Most common site for metastasis from Ca lung* | *: liver (page 521/H)* |
| ϱ *Most common endocrine organ to be involved by metastasis from Ca lung* | *: Adrenals.* |
| ϱ *Ca lung which metastizes to opposite lung* | *: Adenocarcinoma.* |
| ϱ *Commonest tumor to metastise to heart* | *: Ca lung (Bronchogenic Ca)* |
| ϱ *Histological varieties that cavitate* | *: squamous cell and large cell.* |
| ϱ *Histological varieties that are central in distribution* | *: squamous cell and small cell.* |
| ϱ *Histological varieties that are peripheral in distribution* | *: Adenocarcinoma.* |
| ϱ *Pancoost tumor is histologically* | *: squamous cell.* |
| ϱ *Most common variety associated with paraneoplatic syndrome* | *: small cell variety.* |
| ϱ *Most common variety associated with hypokalemia* | *: Small cell (presumably d/t ACTH )* |
| ϱ *Most common variety associated with hypercalcemia* | *: Squamous cell (presumably d/t PTH)* |
| ϱ *Histological variety most responsive to chemotherapy* | *: Small cell* |
| ϱ *Histological variety response to Radiotherapy* | *: Small cell* |
| ϱ *Histological variety associated with best prognosis* | *: Squamous cell* |

**235. Answer is B (Adenocarcinoma):** *Harrison 18th/p 738 Harrisons 17th/551*

***The most common type of lung cancer is Adenocarcinoma***

**Fact to remember:**
*The most common histological type of lung cancer in India is squamous cell carcinoma.*

**236. Answer is A (Variant of large cell Anaplastic Carcinoma):** *Harrison 16th/562-509; Harrison 17th/ 554, 555*

***Oat cell carcinomas are synonymous with small cell carcinomas of lung. Large cell anaplastic carcinoma constitutes an entirely different entity.***

**Characteristic of Small cell carcinoma lung:**

- Usually present as central masses
- Cigarette smoking is an important risk factor and association of smoking with small cell carcinoma lung is high.
- Associated with release of ACTH, AVO, calcitonin, ANF and Gastrin releasing peptide and thus may manifest with hypokalemia (ectopic ACTH).
- Highly malignant tumors with least five year survival rates.
- Highly metastatic lesions with widespread disease at time of diagnosis.
- Management is primarily with chemotherapy with or without radiotherapy
- 90% regression with chemotherapy
- Objective shrinkage in 80% to 90% patients with radiotherapy.
- Surgery is unlikely to be curative because disease is usually widespread at presentation.

**237. Answer is A (Commonest Malignancy of lung):** *Harrison 18th/p 738 Harrisons 17th/551, 552*

***The commonest malignancy of lung is Adenocarcinoma and not small cell carcinoma***

**The most common malignancy of lung is Adenocarcinoma (overall/ world wide)**

*Most common lung cancer worldwide is Adenocarcinoma*
*Most common lung cancer in India is squammous cell carcinoma*
*Most common lung cancer in women is adenocarcinoma*
*Most common lung cancer in smokers is squammous cell carcinoma*
*Most common lung cancer in nonsmokers is adenocarcinoma*
*Most common lung cancer in young patients is adenocarcinoma*
*Most common lung cancer to metastasize is small cell carcinoma*

**Small cell carcinomas are associated with paraneoplastic syndromes**

*Small cell carcinomas are the most common type associated with ectopic hormone production – Robbins 7th/762*

| Ectopic hormones produced by small cell carcinoms | Paraneoplastic syndrome |
|---|---|
| • *ACTH* | *Cushing's syndrome* |
| • *SIADH/ANP* | *Hyponatremia* |
| • *Calcitonin* | *Hypocalcemia* |
| • *Gonadotropins* | *Gynaecomastia* |

**Small cell carcinomas are an established cause for SVC obstruction**
*The most common type of Lung cancer associated with SVC syndrome is small cell carcinoma – Schwartz 8th/562*

**Small cell carcinomas are chemosensitive**
*'Small cell carcinomas are particularly sensitive to radiation and chemotherapy' -Robbins 7th/763*

**Small cell carcinomas commonly present with metastasis to brain (Harrison 16th/508)**
*Small cell carcinomas are aggressive tumors that metastisize widely (>95% patients).*
*Common sites of metastasis include Brain, Bone Liver and Adrenals*

**238. Answer is C (Chemosensitive tumor):** *Harrison 18th/749, 750, 751, 752; Harrison's 17th/ 551,552,553,554; Harrisons 16th/506,507*

***Small cell carcinomas are highly chemosensitive with an overall 90% regression rate with chemotherapy.***

| Property | Small cell Carcinoma | Non small cell Carcinoma |
|---|---|---|
| Location | • ***Central location*** | *Peripheral location* |
| Metastasis | • ***Highly metastatic lesion*** with widespread metastasis at time of diagnosis<br>• Common site of metastasis include brain, bone, Liver and adrenals | Less metastatic than small cell carcinomas |
| Paraneoplastic syndrome | • *ACTH*<br>• *AVP (Vasopressin)*<br>• *Calcitonin*<br>• *ANF*<br>• *Gastrin Releasing peptide* | • ***PTH*** |
| Response to chemotherapy | Superior Response<br>***Overall regression rate is 90%***<br>Rate of complete regression is 30% | Inferior Response<br>*Objective shrinkage in 30-50%*<br>Complete response : uncommon |

**239. Answer is D (Gefitinib is most effective for female smokers with adenocarcinoma on histology):** *Harrison 18th/751; Fishman's Pulmonary Diseases and Disorders 4th/1877; Davidson's 21st/703*

*Gefitinib is an oral 'small molecule Tyrosine kinase Inhibitor' (that inhibit signalling via EGFR) approved for the treatment of patients with NSCCL. Data to support the use of Gefitinib in NSCCL are however diminishing and* ***Gefitinib is most effective in females who have never smoked with adenocarcinoma on histology.***

**Single agent cgemotherapy is prefered for elderly patients (> 70 years)**

*American Society of Clinical Oncology (ASCO)* recommends the use of single agent chemotherapy for elderly patients (> 70 years) with a poor performance status (2003 Guidelines)

*It has however now been stressed (2009 Guidelines) that age alone should not be used to select chemotherapy for patients with advanced NSCLC. Physiological Age (not chronological age) and performance status should be considered when selecting the chemotherapy regimen.*

**Chemotherapy for Advanced (Stage IV) NSCLC**

| **Young patient**<br>Good performance status (PS < 2) | **Elderly patient**<br>Poor performance status (PS ≥ 2) |
|---|---|
| • ***Double agent chemotherapy is preferred for first line therapy***<br>• Platinum based combinations are preferred over non platinum based combinations | • ***Single Agent Chemotherapy is preferred to reduce potential toxicity from chemotherapeutic agents.***<br>• Vinorelbine or docetexal are often used for single agent chemotherapy in the elderly with a poor PS. |

**Gefitinib is most effective for females with adenocarcinoma histology who have never smoked**

Gefitinib is an acceptable second line agent for treatment of patients with advanced NSCLC with adequate performance status when the disease has progressed during or after first line platinum based chemotherapy.

| *Clinical Features that correlate with responsiveness to Gefitinib (Harrison)* |
|---|
| • ***Female Sex*** |
| • ***Never smoking status*** |
| • ***Adenocarcinoma Histology*** |
| • ***Asian Ethinicity*** |

**Contralateral Mediastinal nodes are a contraindication to Surgical Resection**

| *Contraindication to surgical resection in NSCLC (Davidson)* |
|---|
| • *Distant metastasis (M1)* |
| • *Invasion of central mediastinal structures including heart, great vessels, trachea and oesophagus (T4)* |
| • *Malignant pleural effusion (T4)* |
| • ***Contralateral mediastinal nodes (N3)*** |
| • *FEV, < 0.8L* |
| • *Severe or unstable cardiac or other medical condition* |

*N.B. In otherwise fit individual, direct extension of tumour into the chest wall, diaphragm, mediastinal pleura or pericardium or to within 2 cm of the main carina does not exclude surgery. Though surgically resectable, patients with N2 (ipsilateral mediastinal) nodes may require neoadjuvant or adjuvant therapy.*

**Squammous Cell Carcinoma is the most common histological subtype of Lung Cancer in Asia (Including India)**

*Most common lung cancer worldwide is adenocarcinoma*
*Most common lung cancer in India (Asia) is squammous cell carcinoma*
*Most common lung cancer in women is adenocarcinoma*
*Most common lung cancer in smokers is squammous cell carcinoma*
*Most common lung cancer in nonsmokers is adenocarcinoma*
*Most common lung cancer in young patients is adenocarcinoma*
*Most common lung cancer to metastasize is small cell carcinoma*

**240. Answer is B (Small cell carcinoma):** *Ref: Harrison 16th/ 506, 507; Harrison 17th/ 552, 554 Harrison 18th/p 738*

*Cigarette smoking is most strongly associated with squamous cell ca and small cell carcinoma and less commonly with adenocarcinoma.*

Out of squamous cell and small cell carcinomas, the small cell variant is more malignant and metasizes early.

***Thus the option of choice as regards a 'highly malignant' and metastatic lung carcinoma in a chronic smoker is a small cell carcinoma***

| Histological type | Association with smokers | 5 years survival |
|---|---|---|
| **Squamous cell carcinoma** | High | 15 |
| **Small cell carcinoma** | High | 5 (more malignant) |
| **Adenocarcinoma** | Low | 17 |
| **Large cell carcinoma** | Low | 11 |

**241. Answer is B (Growth Hormone):** *Ref: Harrison 14th/ 554, 15th/ 564-5; Harrison 16th/507*

| *Hormones produced by Small Cell variant* | *Hormone produced by non small cell variants* |
|---|---|
| 1. ACTH ♀ | PTH ♀ |
| 2. AVP (Vasopressin) ♀ | |
| 3. Calcitonin ♀ | |
| 4. ANF ♀ | |
| 5. Gastrin releasing peptide ♀ | |

242. **Answer is C (Small cell carcinoma):** *Schwartz 8th 562; Current critical care Diagnosis and treatment 3rd/465*

***The incidence of superior vena caval syndrome is highest with small cell carcinoma.***

Superior vena caval syndrome (SVC syndrome)

- SVC syndrome results from an impedance in outflow from superior vena cava due to external compression
- *The most common cause of SVC syndrome is external compression by a malignant tumour*[Q]
- *The most common malignant tumor causing SVC syndrome is bronchogenic carcinoma*[Q]
- *The most common histological type of bronchogenic carcinoma causing SVC syndrome is small cell carcinoma*[Q]

243. **Answer is B (Oat cell carcinoma):** *Harrisons 16th/506, 507; Harrisons 17th/Limited information*

***Oat cell carcinoma is the other name for small cell carcinoma. Small cells carcinoma respond best to chemotherapy, and they are managed primarily by chemotherapy with or without Radiotherapy.***

*Non small cell carcinomas do not respond as well to chemotherapy as small cell cancers-Harrisons*
*Small Cell Lung cancer (SCLC) is a chemotherapy sensitive disease-H 17th/561*

| Property | Small cell carcinoma<br>*Also called oat cell carcinoma* | Non small cell carcinoma<br>• *Squamous cell carcinoma*<br>• *Adenocarcinoma*<br>• *Large cell carcinoma*<br>• *Bronchoalveolar carcinoma* |
|---|---|---|
| Response to Chemotherapy | ***Superior Response***<br>*Overall Regression rate is 90%*<br>*Rate of complete regression is 30%* | Inferior Response<br>*Overall Regression rate is 40 to 60%*<br>*Rate of complete regression 5%* |
| Response to Radiotherapy | ***Superior Response***<br>*Objective Shrinkage in 80-90%*<br>*Complete response: Often* | Inferior Response<br>*Objective shrinkage in 30-50%*<br>*Complete response: Uncommon* |
| Primary management | *Managed primarily with Chemotherapy with or without Radiotherapy* | *Management primarily with Surgery or Radiotherapy (localized lesions)* |

244. **Answer is C (Small cell Ca of Lung):** *Harrison 16th/ 509; Harrison 17th/ 554 Harrison 18th/p 743*

***'Skeletal connective tissue syndromes including clubbing is usually seen in no n small cell carcinomas'H-16th***
*Clubbing is thus least common with small cell carcinoma of lung*

245. **Answer is B (non small cell carcinoma):** *Read text below: Harrison 16th/ 506-510; 17th/ 552-554; 18th/742, 743*

*Presence of non productive cough, haemoptysis, clubbing and an apical lobe lesion in a sixty year old male suggests a diagnosis of carcinoma lung.*

***Association with clubbing and a peripheral location lead us to a diagnosis of non small cell variant.***

Most common histological variant associated with clubbing : non small cell carcinoma
Most common histological variant presenting at peripheral location : non small cell carcinoma

**Tuberculosis** although, may present with such symptomatology, the age of the patient and non productive nature of cough go against its diagnosis.

246. **Answer is D (Peripheral location):** *Harrison15th/562,563;16th/506;17th/551,552;18th/738 Robbins7th/760; Chandrasoma Taylor 3rd/549*

*'Adenocarcinomas are usually more peripherally located' – Robbins 7th/ 760.*

- Squamous and small cell carcinomas usually present as central masses with endobronchial growths, while adenocarcinomas and large cell cancers tend to present as peripheral nodules or masses frequently with pleural involvement. – *Harrisons 16th/ 507*
- Adenocarcinomas constitute 32% of all lung cancers.
- Adenocarcinomas are the most common form of lung cancer arising in young patients (< 45 years).

**Adenocarcinomas of lungs:**
- Most common histological variant of Bronchogenic carcinoma in the world
- Most common histological variant of Bronchogenic carcinoma in females
- Most common histological variant of Bronchogenic carcinoma in nonsmokers
- Most common histological variant of Bronchogenic carcinoma in young patients

**247. Answer is A and D (More common in females; Peripheral involvement is common):** *Harrison 18th/p 738 Harrisons 17th/552; Robbins 7th/760*

***Adenocarcinoma is the most common form of lung cancer in women and Adenocarcinoma usually presents as a peripheral lesion.***

**Adenocarcinoma is common in females**
Adenocarcinoma is the most common type of lung cancer in women

**Adenocarcinoma is associated with smoking, but may be seen in nonsmokers**
*'All histological types of lung cancer are associated with smoking' - Harrison*
**However** *lung cancer can also occur in individuals who have never smoked and the most common type of lung cancer in life time non smokers is adenocarcinoma*

**Adenocarcinomas are usually more peripherally located** (Robbins 7th/760)
*'Squamous and small cell carcinomas usually present as central masses while adenocarcinoma and large cell cancers tend to present as peripheral nodules or masses' - Harrison*

**248. Answer is B (Adenocarcinoma):** *Ref: Harrison 15th/ 562; Harrison 16th/507; Harrison 17th/551 Harrison 18th/p 738*

***'The most common lung carcinoma arising in life time non smokers in Adenocarcinoma'-Harrisons 16th/507***

**249. Answer is A (Adenocarcinoma):** *Harrisons 17th/554*

**250. Answer is A (Lung):** *Ref: Harrison 14th/ 520; Not elaborated in Harrison 16th; Not elaborated in Harrison 17th*

***The most common site of primary in a patient presenting with secondries to adrenals is Melanoma. Lung and bladder are the second most frequent sites of primary.***
*Amongst the options provided Lung is the single best answer.*

***Most common sites of spread to Adrenals:***

| Primary | Metastatic site (% involvement) |
|---|---|
| Melanoma | 48% |
| Lung | 35% |
| Bladder | 35% |
| Cervix | 31% |
| Colorectum | 31% |
| Breast | 31% |
| Kidney | 20% |
| Ovary | 20% |
| Prostate | 17% |

**251. Answer is C (Oat cell variant is typically associated with hilar adenopathy):** *Harrisons 17th/551, 552; 18th /738*

***Oat cell variant (small cell carcinoma) is typically associated with hilar adenopathy in most cases.***

**Hilar lymphadenopathy is a typical feature of small cell (oat cell) variant**
*'Small cell (oat cell) carcinoma usually occurs in central bronchi with associated mediastinal and hilar adenopathy being a common presentation at time of diagnosis' - Thoracic Imaging: A practical Approach (1998)/72*

*'Small cell (oat cell) carcinoma is associated with significant degrees of mediastinal and hilar adnopathy in most cases'*
*– 'Essential Radiology' by Gunderman (1998)/164*

*'Bilateral bulky hilar adenopathy is typical of oat cell carcinoma'*
*– Clinical Imaging: An Atlas of Differental Diagnosis by Eisenberg (2009)/96 (f)*

**Squammous cell carcinoma accounts for about 30% of lung cancers**

***Adenocarcinoma is the most frequent histological variant of Lung cancer world wide[Q]***

| Histological subtype | Approximate Frequency |
|---|---|
| *Adenocarcinoma* | *~ 32%* |
| *Squammous cell carcinoma* | *~ 29%* |
| *Small cell carcinoma* | *~ 18%* |
| *Large cell carcinoma* | *~ 9%* |

**Cavitation is a feature of squammous cell and large cell variants and not of oat cell/small cell variant**

*'In contrast to squammous cell carcinoma in which central cavitation is noted in 10-20% of cases, small cell cancer rarely cavitates' - Clinical Hematology & Oncology (2003)/945*

| Cavitatory variant | Non cavitatory variants |
|---|---|
| • *Squammous cell (most common)* | • *Small cell* |
| • *Large cell* | • *Adeno carcinoma* |

**Adenocarcinomas present as peripheral masses and not as central masses**

*'Squammous and small cell cancers usually present as central masses while adenocarcinoma and large cell cancers tend to present as peripheral nodule and masses' – Harrison*

| Central location[Q] | Peripheral location[Q] |
|---|---|
| • *Squammous cell*[Q] | • *Adenocarcinoma*[Q] |
| • *Small cell*[Q] | • *Large cell variant*[Q] |

**252. Answer is A (Cough):** *Robbins 7th/763; General Therosis Surgery 6th/1508*

***The most common presenting symptom of lung cancer is cough** – Robbins*

| Common presenting symptoms of lung cancer (Robbins) |
|---|
| ***Cough (75%-Commonest)*** |
| Weight loss (40%) |
| Chest pain (40%) |
| Dyspnea (20%) |

| Common presenting symptoms of lung cancer (General Thoracic Surgery) In decreasing order of frequency. |
|---|
| ***Cough (commonest)*** |
| Hemoptysis |
| Chest pain |
| Dyspnea |
| Wheezing or strider |
| Hoarseness |
| Pleural effusion |
| Superior vena caval syndrome |
| Pancoast tumour |
| Dysphagia |
| Phrenic palsy |

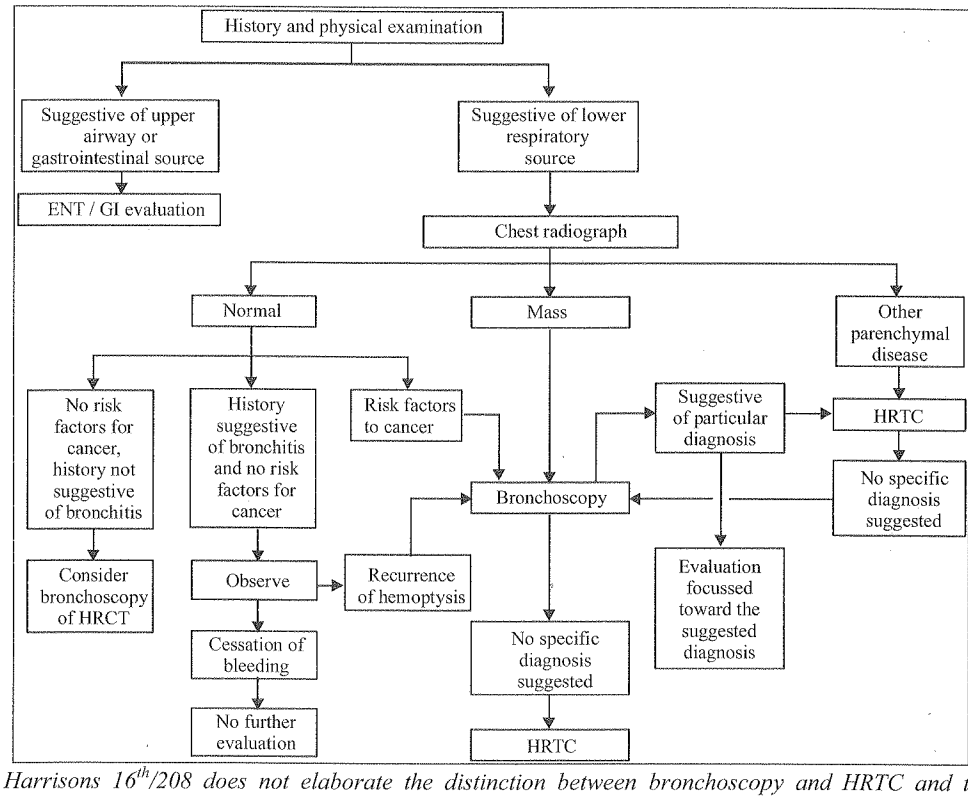
**253. Answer is A (Carcinoma lung):** *Harrison 18th/p 284 Harrison 17th/227*

***The two most common causes for hemoptysis are bronchitis and bronchogenic carcinoma. Bronchitis is not provided amongst the options and hence bronchogenic carcinoma is the single best answer of choice.***
*'Although the relative frequency of the different etiologies of hemoptysis varies from series to series, most recent studies indicate that bronchitis and bronchogenic carcinoma are the two most common causes (in the United States)' - Harrisons*

| Facts to Remember | | |
|---|---|---|
| *The most common cause of Hemoptysis* | : | *Bronchitis and Bronchogenic CA*[Q] *(Bronchitis > Bronchogenic CA)*[Q] |
| *The most common causes of Hemoptysis in India* | : | *Tuberculosis*[Q] |
| *The most common cause of Massive Haemoptysis* | : | *Bronchectasis (World wide)*[Q] *Tuberculosis (India)*[Q] |

**254. Answer is A (Bronchoscopy) :** *Harrison 15th/206; Harrison 16th/208; Harrison 17th/ 228 Harrison 18th/p 286*

***The patient presents a case of hemoptysis with normal X-ray but with risk factors for cancer (Age and history of smoking). Bronchoscopy together with a bronchial or transbronchial biopy is the investigation of choice as indicated in the following algorithm from harrisons text.***




*Algorithm in Harrisons 16th/208 does not elaborate the distinction between bronchoscopy and HRTC and thus reference to previous editions is recommended.*

**255. Answer is B (Bronchoscopy and biopsy) :** *Harrison 14th/555, 198; 15th/206; 16th/208*

***Fibreoptic bronchoscopy with a brochial or transbronchial biopsy is the better option here as it also allows direct visualization of the tumor mass***

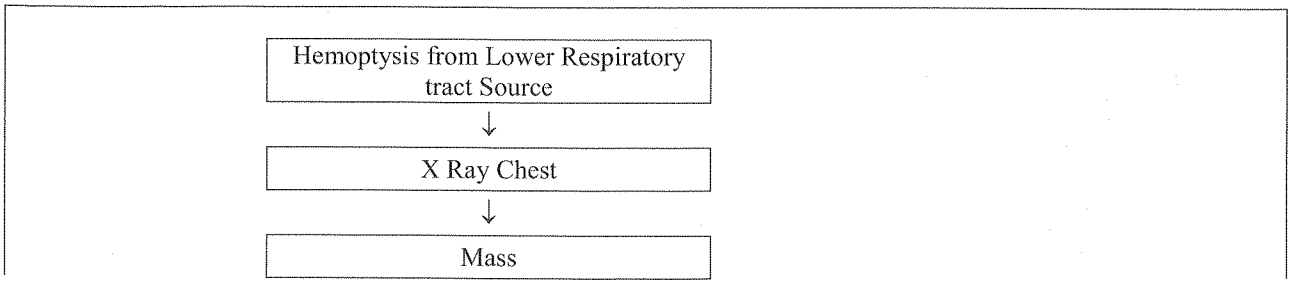
*'The screening of lung cancer by means of sputum cytology & chest radiographs is not very effective'-H14th/255*

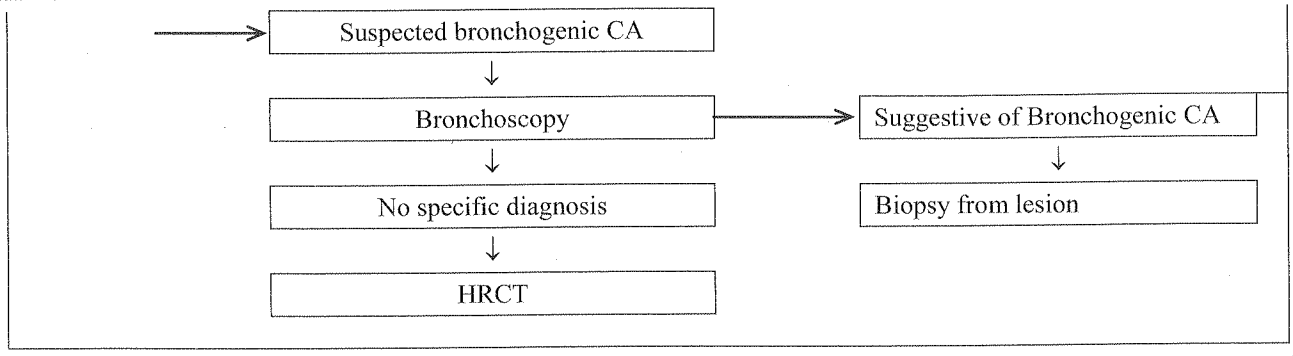
Once signs/symptoms or screening studies suggest a diagnosis of bronchogenic carcinoma it is necessary to establish a tissue diagnosis of malignancy. From the options provided tumor tissues can be obtained by a bronchial or transbronchial biopsy during fibreoptic bronchoscopy or CT guided FNAC. Fibreoptic bronchoscopy is the preferred initial investigation to obtain a tissue diagnosis.

**Approach to diagnosis**

- *The first investigation while investigating a case of haemoptysis*: should be 'X-Ray chest'.
- *Once X-Ray chest suggests bronchogenic carcinoma (i.e. suspected mass)* the next investigation should be Bronchoscopy
- *An HR-CT should be done only if bronchoscopy is negative.*

*In this question* we already suspect the diagnosis of bronchogenic carcinoma. The investigation protocol, therefore expects us to proceed further from this point, hence a bronchoscopy should be the next investigation.
HRCT and guided FNAC is done only if bronchoscopy is negative.
*As TB has already been ruled out sputum cytology is not the investigation to be done.*






**256. Answer is B (Bronchoscopy and biopsy):** *Harrison 14th/555,198; 15th/206; 16th/208; 17th/554,555; Refer algorithm previous question*

*This patient represents a case of suspected bronchogenic carcinoma.* ***Fibreoptic bronchoscopy and biopsy is the investigation of choice*** *as it allows direct visualization of the tumor mass and provides a means of obtaining tumor tissue for histological diagnosis.*
*HRCT is the alternate investigation but should be done if no specific diagnosis is suggested on bronchoscopy.*

**257. Answer is A (Bronchoscopy, lavage and brushing) :** *16th/1507; Repeat*

***The bascic idea is to obtain a tissue biopsy. FNAC could be used, however it would certainly not be the best. Bronchoscopy would allow, both, direct visualization and biopsy, and so is the best option here.***

**258. Answer is A (Bronchoscopy, lavage and brushing) :** *Harrison 16th/1507*

***The basic idea is to obtain a tissue biopsy. FNAC could be used, however it would certainly not be the best. Bronchoscopy would allow, both, direct visualization and biopsy, and so is the best option here.***

**259. Answer is D (Bronchogenic carcinoma) :** *Harrison 16th/2023; Harrison 17th /2140 Harrison 18th/p 2810*

***ACE levels are not elevated in Bronchogenic carcinoma.***

| **Serum levels of ACE may be increased in :** | |
|---|---|
| Sarcoidosis | Hypersensitivity pneumonitis |
| Aesbestosis | Leprosy |
| Silicosis | Lymphoma |
| Berthosis | Tuberculosis |
| Fungal infection | |
| Granulomatous hepatitis | |

**260. Answer is C (surgery):** *Harrison's 15th/565; Oxford text book of surgery IInd/2480, Schwartz 7th/753*

The baffling aspect of the question is that it does not mention whether it is a small cell carcinoma or a non small cell carcinoma as this histological distinction is the bases of the primary modality of treatment.

| Non small cell carcinomas | Small cell carcinomas |
|---|---|
| *For non small cell carcinomas the primary modality depends on the extent of disease*<br>• **Localized diseases: (Stage I & II)**<br>Primary modality of treatment is surgery – **pulmonary resection.**<br>• **Advanced disease:**<br>**Radiotherapy with curative intent** is advocated (± chemotherapy)<br>• **Metastatic disease (Stage IV)** symptomatic/supportive | • *Small cell lung carcinomas behave as systemic disease.*<br>• Most small cell carcinomas have already spread at the time of presentation beyond the bounds of surgery and they are *managed primarily by chemotherapy with or without radiotherapy.* |

If we were to go by the information available in the question,

- **The maximum tumor size (T) is = 5 cm (≥ 3), i.e. $T_2$**
- **There is no nodal involvement (No)**
- **There is no distal metastases (Mo)**

**Thus it is $T_2$ $N_0$ $M_0$ disease or stage I disease**

***The treatment of choice for stage I disease is surgery i.e. Pulmonary resection***

- The tumor in question has no nodal involvement and no metastases and hence is likely to be a non small cell carcinoma.
  *Further, according to oxford textbook of surgery 2nd/2480*
- "Recent data suggest that staging small cell lung cancer using TNM system employed for non small cell carcinomas may be helpful. For patients with stage I disease surgical resection and postoperative adjuvant chemotherapy provides a better prognoses than non surgical therapy".

*Thus within the limits of information provided the primary modality of treatment here should be surgery.*

| | | 5 Year Survival Rate, % | |
|---|---|---|---|
| **Stage** | **TNM Descriptors** | **Clinical Stage** | **Surgical Pathologic Stage** |
| IA | T1 N0 M0 | 61 | 67 |
| IB | T2 N0 M0 | 38 | 57 |
| IIA | T1 N1 M0 | 34 | 55 |
| IIB | T2 N1 M0 | 24 | 39 |
| IIB | T3 N0 M0 | 22 | 38 |
| IIIA | T3 N1 M0<br>T1-2-3 N2 M0 | 9<br>13 | 25<br>23 |
| IIIB | T4 N0-1-2 M0<br>T1-2-3-4 N3 M0 | 7<br>3 | <5<br><3 |
| IV | Any T any N M1 | 1 | <1 |

| **Tumor (T) status descriptor** | |
|---|---|
| T0 | No evidence of a primary tumor |
| TX | Primary tumor cannot be assesed, or tumor proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy. |
| TIS | Carcinoma is situ |
| T1 | Tumor > 3 cm in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than lobar bronchus (i.e. not in main bronchus) |
| T2 | Tumor with any of following: > 3 cm in greatest dimension: inolves main bronchus, >= 2 cm distal to the carina: invades visceral pleura; associated with atelectasis or obstructive pneumonitis extending to hilum but does not involve entire lung. |
| T3 | Tumor of any size that directly invades any of the following: chest wall (including superior sulcus tumors), diaphragm, mediastinal pleura, parietal pericardium; or tumor in main bronchus < 2 cm distal to carina but without involvement of carina; or associated atelectasis or obstructive pneumonitis of entire lung. |
| T4 | Tumor of any size that invades any of the following: mediastinum, heart, great vessels, trachea, esophagus, vertebral body, carina or tumor with a malignant pleural or paericardial effusion, or with satellite tumor nodule(s) within the ipsilateral primary-tumor lobe of the lung. |

| **Lymph node (N) involvement of descriptor** | |
|---|---|
| NX | Regional lymph nodes cannot be assessed |
| N0 | No regional lymph node metastasis |
| N1 | Metastasis to ipsilateral peribronchial and/or ipsilateral hilar lymph nodes, and intrapulmonary nodes involved by direct extension of the primary tumor. |
| N2 | Metastasis to ipsilateral mediatinal, contralateral lymph node(s) |
| N3 | Metastasis to contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s) |

| **Distant metastasis (M) descriptor** | |
|---|---|
| MX | Presence of distant metastasis cannot be assessed |
| M0 | No distant metastasis |
| M1 | distant metastasis present |

**261. Answer is D (Hypercalcemia):** *Ref: Harrison 15th/ 2209, 280; Harrison 2252, 2257; Harrison 17th/ 2380, 554 Harrison 18th/p 3100, 743*

***Presence of polyuria, abdominal pain, and general symptoms such as nausea, vomiting and altered sensorium in a patient with bronchogenic carcinoma suggest a diagnosis of hypercalcemia secondary to paraneoplastic syndrome from PTH related peptide production.***

The symptomatic profile of this patient matches with that of hypercalcemia

**Manifestations of Hypercalcemia**

| General | Renal feature | Bones | Abdomen | Cardiac | Calcification |
|---|---|---|---|---|---|
| • Anorexia<br>• Nausea<br>• Vomiting<br>• Fatigue<br>• Mental confusion (≅ altered sensorium) | • Polyuria* & Nocturia<br>• Renal colic from stones | • Bone pain<br>• When cause is hyperparathyroidism<br>• Bone cysts<br>• Brown tumors | • Abdominal pain (peptic ulceration)<br>• Constipation | • Short QT interval in ECG & in some patients cardiac arrythmias | Ectopic calcification & chondrocalcinosis |

* **Polyuria** results from effect of hypercalcemia on renal tubules reducing there concentrating ability a form of nephrogenic diabetes insipidus

**262. Answer is D (Superior Vena cava obsrtuction) :** *Read text below; Harrison's 15th/642*

***The patient in question is presenting with classical signs and symptoms of superior mediastinal syndrome or Superior vena caval syndrome.***

***Lung cancer is the commonest cause of superior vana caval syndrome or SVC obstruction. As the options provided include superior vena caval obstruction as a distinct entity, it is the option of choice.***

**Clinical manifestations of obstruction to SVC :**

| Symptoms | Signs |
|---|---|
| • ***Swelling around neck & face*** especially around the eyes<br>• ***Dyspnea***<br>• Cough<br>• Others: Hoarseness / Headache / Tongue swelling / Nasal congestion / Epistaxis Haemoptysis / Dysphagia / Pain / Dizziness / Syncope | • Dilated neck veins<br>• ***Increased number of collateral veins over anterior chest wall***<br>• Cyanosis<br>• Edema of face, arms & chest<br>• Proptosis, glossal and Laryngeal edema and obtundation in severe cases |

*Symptoms are aggrevated by bending forwards and lying down.*

**263. Answer is B (Small cell carcinoma):** *'Clinical Hematology and Oncology' by Furie (2003) 1st/99; Schwartz 8th/562; Current Critical Care Diagnosis & Treatment 3rd /465*

***The incidence of superior vena caval syndrome is highest with small cell carcinoma.***

Superior vena caval syndrome (SVC syndrome)

- SVC syndrome results from an impedance in outflow from superior vena cava due to external compression
- *The most common cause of SVC syndrome is external compression by a malignant tumour*[Q]
- *The most common malignant tumor causing SVC syndrome is bronchogenic carcinoma*[Q]
- *The most common histological type of bronchogenic carcinoma causing SVC syndrome is small cell carcinoma*[Q]

**Etiologies of Superior Vena Cava Obstruction:**

| Malignancy | 95% |
|---|---|
| *Lung Cancer* | *65%* |
| *Lymphoma* | *15%* |
| *Breast cancer* | *5%* |
| *Germ-cell* | *2%* |
| *Thymic cancer* | *2%* |
| *Other cancer* | *4%* |

| Benign | 5% |
|---|---|
| *Central venous device related* | *1%* |
| *Mediastinal fibrosis* | *3%* |

## Cyststic Fibrosis

**264. Answer is D (Endocrine):** *Refere text below*

***Cystic fibrosis is typically charachterized by Exocrine Pancreatic insufficiency.***
***Endocrine Pancreatic insufficiency is not seen as a tyical manifestation of cystic fibrosis.***

**Charachteristic Classical Manifestations of Cystic Fibrosis**
(Typical System Involvement)

| Respiratory system (Sinopulmonary disease) | Gastrointestinal System (Intestinal; Hepatobiliary; Pancreatic) | Genitourinary System (Male Infertility) |
|---|---|---|
| • Pulmonary infection<br>Persistant colonization/infection with typical cystic fibrosis pathogens, including Staphylococcus aureus, nontypeable, Hemophilus influenzae, ***mucoid and nonmucoid Pseudomonas aeruginosa***, Burkholderia cepase<br>• Chronic obstructive Pulmonary Disease<br>• Bronchiectasis is typical<br>• Airway obstruction manifested by wheezing and air trapping<br>• Chronic cough & sputum production<br>• Digital clubbing<br>• Persistent chest radiograph abnormalities (eg. Bronchiectasis, atelectasis, infiltrates, hyperinflation)<br>• Nasal Polyps<br>radiographic or computed tomographic abnormalities of paranasal sinuses | Intestinal<br>meconium ileus, distal intestinal obstruction syndrome, rectal prolapse.<br>Pancreatic<br>Pancreatic exocrine deficiency<br>Hepatobiliary<br>Hepatic disease manifested by clinical or histologic evidence of focal biliary ***cirrhosis***, or multilobular ***cirrhosis***<br>Nutritional<br>Failure to thrive (protein-calorie malnutrition), hypoproteinemia, edema, complications secondary to fat-soluble vitamin deficiency | Male urogenital abnormalites resulting in obstructive azoospermia are typical |

**Metabolic Abnormalities** are typically charachterized by **salt depletion syndrome**,
*(Hyponatremia, Hypocholeremia and Hypokalemic Metabolic Alkalosis)*

**265. Answer is A (Pseudomonas Aeroginosa):** *Cystic Fibrosis' (Oxford University Press)2000/31*

***The most common cause of Pulmonary infections in cystic fibrosis is Pseudomonas aeroginosa***

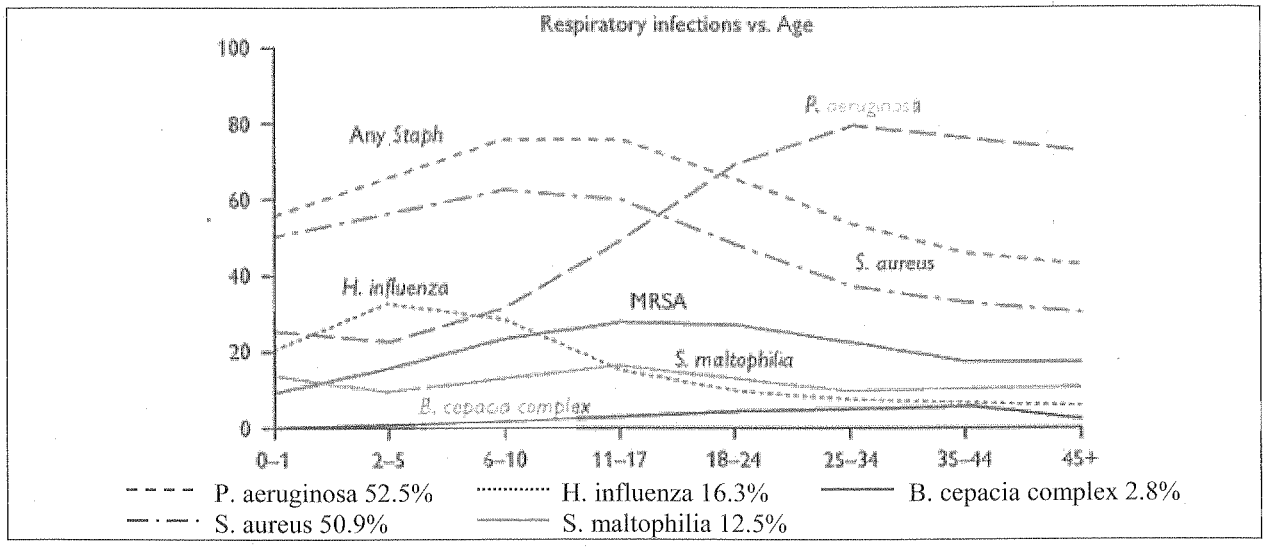
*'The most common pathogen in CF is Pseudomonas Aeroginosa followed by Staphylococcus'*
*- 'Pseudomonsa:Gemmu & Molecular Biology' (Harizon Scientific Press)2008/160*

**Pulmonary Infection in Cystic Fibrosis**

- *The most common cause of Pulmonary infection in cystic fibrosis in children is staphylococcus aureus*[Q]
- *The most common cause of Pulmonary infection in cytic fibrosis in adolescents and adults is Pseudomonas Aeroginosa.*
- The two most common cause of pulmonary infection in cystic fibrosis are staphylococcus aureus and Pseudomonas Aeroginosa.

***Overall (all age groups) Pseudomonas Aeroginosa is marginally more common than staphylococcus aureus as a cause of pulmonary infection in cystic fibrosis.***

- *The most common organism causing chronic lung disease in patients with cystic fibrosis is pseudomonas aeroginosa*




**266. Answer is A (Staphylococcus Aureus):** *Imaging in Pediatric Pulmonology (Springer) 2012/313*

***Staphylococcus Aureus (Methicillin sensitive) are the most common pathogen isolated in sputum of children with cystic fibrosis during the first decade.***

*'The most prevalent pathogen to cause pulmonary infection in cystic fibrous during childhood is staphylococcus aureus. Pseudomonas aeroginosa becomes the most common organism in adolescents and adults. Hemophilus influenza is also seen in early life (2-5 years) and its frequency decreases with age. Bukholderia capacia is also infrequent but its incidence increase with age. Stenotrophomonos is an infrequent organism seen at any age.*

*– USMLE Step III: Review/Q1 Case 7*

*'The most common cause of pneumonia in a patient with cystic fibroses is Pseudomonas aeroginosa, but initial infection is most often due to staphylococcus aureus'- Microbiology: Pearls of Wisdom' by Booth (Jones & Barlett) 2000/203*

**267. Answer is D (Sweat chloride> 60):** *Cystic fibrosis (CF) Foundation; European best practice guidelines for cystic fibrosis neonatal screening*

**Sweat chloride levels > 60 mmol/L strongly suggest a diagnosis of Cystic Fibrosis.**

*Sweat chloride levels > 60 mmol/L of chloride is sweat is considered diagnostic of Cystic fibrosis (when 1 or more other criteria are present). In neonatal screening, a diagnosis of CF can be made when chloride levels exceed 60 mmol/L, and excluded when they are below 30 mmol/L.*

| Interpretation based on Sweat Chloride Levels | Chloride level for infants up to and including 6 months of age | Chloride level for people older than 6 months of age |
|---|---|---|
| **CF is very unlikely** | Equal to or less than 29 mmol/L | Equal to or less than 39 mmol/L |
| **CF is possible** | Between 30 - 59 mmol/L (intermediate) | Between 40 - 59 mmol/L (intermediate |
| **CF is likely to be diagnosed** | Greater than or equal to 60 mmol/L | Greater than or equal to 60 mmol/L |

**268. Answer is D (Bronchocoele):** Radiological Society of North America Official Publication

***Finger in glove sign results from mucoid impaction within branching airways (Bronchocoele) from any cause. Although Finger and glove sign may be seen in ABPA, cystic fibrosis and tubercular bronchiectasis, the presence of Finger in Glove Sign essentially indicates mucus impaction or Bronchocoele formation from these causes. Bronchocoele is therefore the single best answer***

The finger in glove sign can be seen on either chest radiograph or CT chest and refers to the characteristic sign of mucoid impaction along large branching airways (Bronchocoele). A Bronchocoele refers to a mucous-plug-filled

dilated bronchi surrounded by aerated lung. Finger in glove sign may be seen in several conditions that lead to the formation of Bronchocoele including ABPA, Cystic Fibrosis, Bronchiectasis, Endobronchial tumors or Bronchial atresia

Mucoid impaction within branching airways (Bronchocoele) is a relatively common finding at chest radiography and computed tomography (CT). Both congenital and acquired abnormalities may cause mucoid impaction of the large airways that often manifests as tubular opacities known as the finger-in-glove sign. The congenital conditions in which this sign most often appears are segmental bronchial atresia and cystic fibrosis. The sign also may be observed in many acquired conditions, include inflammatory and infectious diseases (allergic bronchopulmonary aspergillosis, broncholithiasis, and foreign body aspiration), benign neoplastic processes (bronchial hamartoma, lipoma, and papillomatosis), and malignancies (bronchogenic carcinoma, carcinoid tumor, and metastases)

## Bronchial Adenoma and Bronchial Cysts

**269. Answer is A (Recurrent haemoptysis):** *Harrison 14th/561; 15th/570-71; 16th/515; 17th/ 562; Harrison 18th/p 753*

***Bronchial adenomas are hypervascular, and can bleed profusely. Recurrent haemoptysis is the most common manifestations.***

| **Bronchial adenomas include:** |
|---|
| Carcinoids : 80-90% |
| Adenocystic tumors (cylindromas): 10 to 15%) |
| Mucoepidermoid tumors : 2-3% |

Broncheal adenomas are hypervascular, and can bleed profusely. Recurrent haemoptysis is the most common manifestations. Others being, chronic cough, obstruction with atelectasis, lobar collapse, pneumonitis and abscess formation.

**270. Answer is B (Most common site is mediastinum):** *Rudolph's Fundamentals of Pediatrics 3rd/716*

*Most common site of bronchial/bronchogenic cysts is mediastinum. Only about 15% of bronchogenic cysts occur in the lungs (pulmonary bronchial cysts). Pulmonary bronchogenic cysts often become infected. Bronchogenic cysts are benign lesion and do not have malignant potential (not premalignant).*

### Bronchial Cyst/Bronchogenic cysts: Review

- Bronchial cysts represent islands of bronchial tissue left behind during the branching of the airways during early fetal development.
- They arise due to abnormal budding of the tracheobronchial tree and foregut and are lined by bronchial epithelium.
- ***The most common site of bronchial cysts is mediastinum.***
- *The other site of bronchial cyst is within the pulmonary parenchyma (lung) (Less common site – 15%)*

| Mediastinal bronchial cyst | Pulmonary parenchymal cyst (lungs) |
|---|---|
| • ***Most common site for bronchial cysts*** | • Less common site (- 15%) |
| • Most common site is middle mediastinum | • Most common site is the lower lobes |
| • Commonly arise when bronchial tissue is separated from airways early in gestation | • Commonly arise when bronchial tissue is separated from airways late in gestation |
| • Communication with tracheobronchial tree is rare | • Communication with tracheobronchial tree is more common than with mediastinal cysts. |
| | • ***These cysts often become infected.*** |

- Most bronchogenic cysts are asymptomatic and discovered as incidental radiographic findings in a young adult.
- When symptoms do occur they result most commonly from infection.

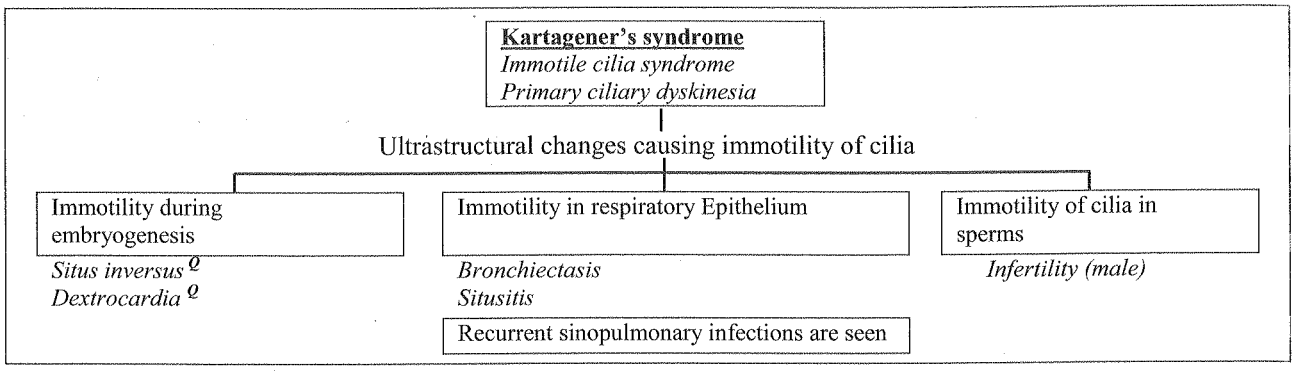
***Pulmonary parenchymal cysts often become infected*** – *Rudolph*

- ***Bronchogenic cysts are not considered premalignant lesions. However according to Rudolph's textbook there is a small risk of malignant change and the best approach is removal and histological examination.***

## Kartagener's Syndrome

**271. Answer is C (Mental retardation):** *Robbins 7th/727; Harrisons (old edition) 11th/940, 1082*

*Mental Retardation is not a feature of Kartagener's syndrome.*




**272. Answer is E (Cystic fibrosis):** *Harrisons 17th/1629 (not eloborated): Harrison 11th/1082, 940 Robbins 7th/727*

***Kartagener's syndrome is associated with situs inversus, sinusitis, infertility and bronchiectasis***

| Syndrome | Major cardiac Anomaly | Major non cardiac anomaly |
|---|---|---|
| *Kartagener's syndrome*<br>*(Immotile cilia syndrome)*<br>*(Primary ciliary dyskinesia)* | *Dextrocardia Q* | • *Situs inversus Q*<br>• *Sinusitis Q*<br>• *Bronchiectasis Q*<br>• *Infertility Q* |

**Note**

*Situs inversus refers to perfect mirror image of normal physiologic position of visceral organs with preservation of their A-P relationship. Situs inversus is usually associated with dextrocardia (Heart on Right Side of chest).*

## Pulmonary Renal Syndrome

**273. Answer is D (All of the above):** *Acute Renal failure in Practice' 1st/345; Oxford Testbook of clinical Nephrology 3rd/582*

***Laptosporiasis, hanta virus infection and Paraquat poisoning may all cause Pulmonary Renal syndrome***

**Differential diagnosis of the "pulmonary- renal syndrome"**

**Lung haemorrhage and glomerulonephritis**

- *ANCA-associated vasculitis*
  - *Wegener's granulomatosis*
  - *Microscopic polyarteritis*
  - *Churg Strauss Syndrome*
  - *Renal Limited vasculitis*
- *Anti-GBM disease – Good posture's syndrome*
- *Cryoglobulinemic vasculitis*
- *Henoch-Schonlein purpura*
- *Bechet's syndrome*
- *Systemic lupus erythematosus, RA, systemic sclerosis, Polymyositis and other connective tissue disorders*

**Pulmonary infections with renal failure**

- *Any severe pneumonia with ATN*
- *Legionella*
- *Hantavirus*
- *Leptospirosis*

**Severe pulmonary oedema associated with renal failure of any cause**

- *RPGN*
- *Idiopathic immune complex GN*

**Pulmonary emboli with IVC thrombosis**

**Paraquat poisoning**

**274. Answer is A (Goodpasture's syndrome):** *Refer text below; Current Diagnosis and Treatment in Pulmonary Medicine 1st (2003)/211*

***Association of hematuria and hemoptysis suggest a diagnosis of Goodpasture's syndrome.*** *ANCA antibodies are usually negative but may be present in upto 30% of patients*

**Good pasture's syndrome**

Good pasture's syndrome is an autoimmune disease characterized by formation of Anti GBM antibodies that attack both pulmonary capillaries and the Glomerulus (GBM)

*Preceding Resp infection*
*Toxic lung exposure*
*Drug exposure Etc*

*Antibodies against Non collagenous Domain (NCL) of α3 chain of collagen type IV*
*(Found in Glomerular Bacement membrane & Pulmonary capillaries)*

Serology

- *Circulating Anti GBM antibodies (IgG): Positive*
- *ANCA antibodies: Typicallyy negative (May be present in upto 30% of patients)*
- *ANA antibodies : usually normal*
- *C3 levels : Usually normal*

Two Age Groups

- *Young men in late 20's (Men >> females)*
- *Men and women their 60-70's*

**Antibodies agonist Glomerular Basement Membrane (GBM)**

**Glomerulonephritis /Renal Disease**

- Features of Acute Glomerulonephritis (RPGN)
  *Hematuria*[Q]
  *Proteinuria*[Q]
  Edema
  *Rapidly progressive renal failure*[Q]
- Pathological Picture[Q]
  *Diffuse crescenteric Glomerulonephritis*[Q]
  *Linear IgG*[Q] *staining along basement membrane on immunofluorescence*[Q]

*Dysmorphic RBC and RBC cast are present in urine suggesting Glomerulonephritis*[Q]

**Antibodies against pulmonary capillaries**

**Pulmonary /Lung Manifestations**

Clinical

- Hemoptysis (Frank)
  *Hemoptysis is largely confined to smokers*
- Dyspnea

X-Ray finding[Q]

- *Diffuse bilateral pulmonary infiltrates*[Q]

**Goodpasture's syndrome and ANCA**

*ANCA is typically negative in Goodpastures syndrome and it is classified as an ANCA negative vasculitis*
*Nevertheless*
*ANCA seropositivity may occur in upto 30 percent of patients with Goodpasture's syndrome.These patients with ANCA have subtle signs of a systemic vasculitis and represent an overlap between goodpastures and either Wegener's granulomatosis (WG) or Microscopic polyangitis(MPA)-Current Diagnosis and Treatment in Pulmonary Medicine 1st (2003)/211*

**275. Answer is A (Good pasture's syndrome):** *Current critical cace diagnosis & Treatment 3rd*
***Association of hematuria and hemoptysis suggests a diagnosis of Goodpasture's syndrome***

*Good pasture's syndrome is an autimmune disease charachterized by formation of Anti GBM antibodies, that attack both the pulmonary capillaries (hemoptysis) and the glomerulus (hematuria).*
*The classical presentation is that of a young male smoker with signs of acute glomerulonephritis (hematuria, proteinuria & RBC cast) and hemoptysis associated with bilateral pulmonary infiltrates.*

## Neonate Alveolar Proteinosis

**276. Answer is A (Neonatal Alveolar Proteinosis):** *Nelsons 18th/ 1821; Pediatric Imaging by Siegel and Coley (2005)/101*

***The child in question is presenting with characteristic features of Neonatal Pulmonary Alveolar Proteinosis (PAP).***
*Familial cases of Neonatal Pulmonary Alveolar Proteinosis have been observed and a genetic basis has been suggested.*
*None of the other options have a familial basis and hence neonatal PAP is the single best answer of choice.*
*TAPVC is unlikely as ECHO is unremarkable and TAPVC does not have a familial basis.*

*Meconium aspiration syndrome is unlikely as it does not have a familial basis and the question provides no other clinical clues to suggest meconium aspiration such as meconium staining*
*Congenital Herpes infection has an entirely different mode of presentation and can be safely excluded.*

**Pulmonary Alveolar Proteinosis (PAP)**

- PAP is a disorder characterized by the intra-alveolar accumulation of pulmonary surfactant proteins

| Etiology |
|---|
| • Defect in surfactant proteins (SP) (SP –B & SP –C) |
| • Defect in colony stimulating factor receptor (GM –CSF) gene |
| • Defect in ATP – binding cassette transporter Gene (ABCA3 |

- ***It may present in neonates*** (Neonatal PAP) and in older infants, children and adults

| Neonatal (Congenital PAP) | PAP in older children and Adults (Adult PAP) |
|---|---|
| This has a fulminant course and is often fatal | This has a gradually progressive course |

*(Note that the neonatal and adult forms are distinct entities and have different etiologies and manifestations)*

- ***Familial cases have been observed and a genetic basis (****Autosomal recessive****) has been suggested for neonatal congenital PAP.***
  No Gender difference in frequency has been observed.
- *Neonatal PAP presents with severe* ***respiratory distress in the neonatal period.***
- ***Radiological features resemble those of hyaline membrane disease and may show fine reticulonodular infiltrates radiating from the hilum.***
- *It* ***has a fulminant course and leads to death from rapidly developing respiratory failure.***

**277. Answer is C (Neonatal pulmonary alveolar proteinosis):** *Repeat. Refer previous question*

## Symptoms and Signs of Respiratory Disease

**278. Answer is B (Empyema):** *Harrisons 16th/208; Harrisons 17th/227 Harrison 18th/p 284, 285*

***Empyema by itself is not a cause for hemoptysis.***

*Pneumonia, Mitral stenosis and Bronchiectasis are established causess for hemoptysis.*

Differential Diagnosis of hemoptysis

| Tracheobronchial source | Pulmonary parenchymal source |
|---|---|
| • Neoplasm (branchogenic carcinoma, endobronchial metastatic tumor, Kaposi's sarcoma, bronchial carcinoid)<br>• Bronchitis (acute or chronic)<br>• ***Bronchiectasis***<br>• Broncholithiasis<br>• Airway trauma<br>• Foreign body | • Lung abscess<br>• ***Pneumonia***<br>• Tuberculosis<br>• Mycetoma ("fungus ball")<br>• Goodpasture's syndrome<br>• Idiopathic pulmonary hemosiderosis<br>• Wegener's granulomatosis<br>• Lupus pneumonitis<br>• Lung contusion |
| **Primary vascular source** | **Miscellaneous/rare causes** |
| • Arterivenous malformation<br>• Pulmonary embolism<br>• ***Elevated pulmonary venous pressure (esp. mitral stenosis)***<br>• Pulmonary artery rupture secondary to balloon- tip pulmonary artery catheter manipulation | • Pulmonary endometriosis (catamenial hemoptysis)<br>• Systemic coagulopathy or use of anticoagulants or thrombolytic agents |

**279. Answer is A (Cavity):** *'Textbook of practical physiology' by Pal (Orient Longman) 2001/171*

***Cavernous Respiration (Cavernous Breathing) is a low pitched bronchial breath sound heard over a cavity which is situated superficially and communicates with a patent bronchus.***

**Bronchial breath sounds**

The bronchial breath sound originates in the larger airways and are transmitted directly to the chest wall without passing through the alveoli. The sound passing through the lung tissue is not modified and auscultated like bronchial sounds from the chest walls. This sound resembles the sound obtained by listening over the trachea (directly placing a stethoscope on the trachea).

*The characteristics of these sounds are:*

1. Duration of expiration is equal to or longer than that of inspiration.
2. Intensity of expiration is more than that of inspiration.
3. There is a definite gap between inspiration and expiration.
4. Sounds are harsh or aspirate in nature.
5. They are high-pitched with frequencies above 600Hz.

**Bronchial Breath Sounds**

Bronchial breath sounds are of three types: tubular, cavernous, and amphoric.

| Tubular Bronchial Breath sound | Cavernous Bonchial Breath sound | Amphoric Bronchial Breath sound |
|---|---|---|
| The tubular bronchial breath sound is a high pitched sound resulting from the passage of vibrations produced in the small bronchi directly to the chest wall through a solid lung tissue. This is seen when the lung parenchyma becomes a solid mass, as in consolidation. | The cavernous bronchial breath sounds is a low pitched bronchial breath sound heard over a cavity, which is situated superficially and communicated to a patent bronchus. The size of the cavity should be more than 2 cm in diameter to produce a cavernous breath sound. | The amphoric bronchial breath sounds is a high pitched bronchial sound that resembles the sound produced by blowing air into a wide-mouthed bottle. This is heard over a very large cavity communicating pneumothorax. It is also seen in large pulmonary cysts having communication with a patent bronchus. |



**280. Answer is D (Tracheal shift to side of consolidation):** *Text below*

***Trachea stays in midline in consolidation (no mediastinal shift).***

*Consolidation is usually caused by pneumonia. In this situation alveoli are full of inflammatory exudates but the size of the lung is unaffected so the trachea remains in its normal midline position.*

| | Tracheal deviation (Mediastinal shift) | Chest expansion | Percussion note ↓ Duller ↑ Hyper-resonant | Breath sounds ↑ Louder ↓ Softer | Added sounds | Vocal resonance |
|---|---|---|---|---|---|---|
| **Consolidation** | No | Normal, or↓ | Normal, or↓ | ↑ (Bronchial) | Coarse crackles +/- rub | ↑ Whispering Pectoriloquy |
| **Lobar collapse** | Yes (Towards collapse) | ↓ | ↓ | ↓ | No | ↓ |
| **Pleural effusion** | No | ↓ | ↓ (Stony dull) | ↓ | Occasional rub | ↓ |
| **Pneumothorax** | Yes (Specially with tension) | Normal or↓ | ↑ | ↓ | Occasional click | ↓ |

**281. Answer is A (Iatrogenic Pneumothorax):** *Refer text below; 'Complications in Anesthesiology' by Kirby (2007)/169*

***Subclavian vein cannulation is an important cause of iatrogenic pneumothorax. Absence of breath sounds and Hyper-resonance of chest wall on percussion alongwith sudden breathlessness after attempted subclavian vein cannulation suggests a diagnosis of Iatrogenic Pneumothorax.***

Common causes of Iatrogenic Pneumothorax (Decreasing order of frequency)

*Transthoracic Needle Lung Biopsy*
***Subclavian vein cannulation***
*Thoracocentesis*
*Pleural Biopsy*
*Positive Pressure ventilation*

**Iatrogenic Pneumothorax**

| History |
|---|
| • History of Procedure known to cause iatrogenic pneumothorax (subclavian vein cannulation) |
| • Sudden onset Breathlessness |
| • Chest discomfort / chest pain |

| Examination |
|---|
| Inspection/ palpatum |
| • Reduced movements over affected side |
| • Mediastinal shift to opposite side |
| • Decreased vocal fremitus |
| Percussion |
| Hyper-resonant |
| Auscultation |
| Diminished or absent breath sound |

**282. Answer is A (Tracheobronchial tree):** *Harrison 17th /227*

***The most common source of hemoptysis is the tracheobronchial tree.***
***The most common site of hemoptysis within the tracheobronchial tree are small to medium sized airways.***

*'The most common site of bleeding is the tracheobronchial tree'* Q *- Harrison's 17th/227*
*'The most common site of hemoptysis is bleeding from the small to medium sized airways'* Q *- Harrison's 18th/284*

**283. Answer is A (Bronchial Artery):** *Harrison 17th /227; Harrison's 18th/285*

***The most common source of bleeding in massive hemoptysis are the Bronchial arteries which are part of the high pressure systemic circulation***

*'The most common source of bleeding in hemoptysis is the tracheobronchial tree which can be affected by inflammation (bronchitis, bronchiectasis) or neoplasm (bronchiogenic carcinoma, endobronchial metastatic carcinoma or bronchial carcinoid tumor). The bronchial arteries which originate from either the aorta or from intercostal arteries, and are therefore part of the high pressure systemic circulation are the source of bleeding in bronchitis, bronchiectasis or with endobronchial tumors'- Harrison's 17th/227*

*'While alveolar haemorrhages arise from capillaries that are part of the low pressure pulmonary circulation,bronchial bleeding is generally from bronchial arteries which are under systemic pressure and therefore predisposed to large volume bleeding' - Harrison's 18th/284*

**284. Answer is A (Mitral Stenosis):**

***Pulmonary apoplexy refers to sudden severe haemoptysis that may be seen in patients with Mitral Stenosis from rupture of a bronchial vein.***

**Different kinds of classical hemoptysis described in mitral stenosis:**

- *Sudden profuse hemorrhage (pulmonary apoplexy)* results from the rupture of thin-walled dilated bronchial veins. It is more common early in the disease before bronchial veins thicken and are able to withstand the raised pressure. Often profuse
- *Pink Frothy sputum* of pulmonary edema.
- *Blood-stained sputum* associated with attacks of paroxysmal nocturnal dyspnea.
- Pulmonary infarction, which is a late complication of long-standing MS associated with heart failure

| Causes of Haemoptysis in Mitral stenosis |
|---|
| Pulmonary apoplexy (rupture of thin walled bronchial veins) |
| Acute pulmonary oedema |
| Pulmonary infarction |
| Winter bronchitis |
| Pulmonary haemosiderosis |

**285. Answer is A (Central cyanosis becomes evident when reduced Hb < 5g/dl):** *Harrison 18th/p 288, 289 Harrisons 17th/230*

*Cyanosis (both central and peripheral) become evident when the amount of reduced Hb exceeds 5g/dl (becomes >5gm/dl) and not when reduced Hb is less than 5g/dl.*

**Cyanosis becomes evident when Reduced Hb exceeds 4-5g/dl**

*'Cyanosis becomes evident when reduced Hb exceeds 5g/dl'- Wintrobe's 6th/ 194; CSDT 3rd/19; Guyton 6th/535*
*'Cyanosis becomes evident when reduced Hb exceeds 4g/dl'- Harrisons 17th/230*

**Pulmonary diseases such as chronic Asthma, Alveolar hypoventilation and Hemoglobin disorders like methemoglobinemia all cause central cyanosis**

**Cyanosis**

Cyanosis is bluish discolouration of skin and mucous membrane that appears when the capillary content of reduced hemoglobin is greater than 5g/dl (Robbins, CSDT, CPDT old editions)

*According to Harrisons 17th edition cyanosis is said to become apparent when reduced Hb > 4g/dl*

| Central cyanosis | Peripheral cyanosis |
|---|---|
| • Central cyanosis is caused by in adequate oxygenation of systemic arterial blood due to decreased arterial oxygen saturation or Hemoglobin abnormalities | • Peripheral cyanosis is caused by slowing of blood flow and increased extraction of oxygen from normally saturated blood |
| • It results from cardiac shunting, pulmonary diseases or hematological disorders (Hb abnormalities) | • It results from vasoconstriction or decreased peripheral blood flow, reduced cardiac output or vascular occlusion |
| • *Central cyanosis is charachterized by cyanosis affective both mucous membranes and skin* | • *Peripheral cyanosis is characterized by cyanosis of skin alone and sparing of mucous membranes* |
| Causes | Causes |
| **Decreased arterial oxygen saturation** | • Vascular occlusion |
| • Decreased atmospheric pressure – high altitude | - Arterial obstruction |
| • Impaired pulmonary function | - Venous obstruction |
| - ***Alveolar hyoventilation*** | • Reduced cardiac output |
| - ***Uneven relationships between pulmonary ventilation and perfusion*** (perfusion of hypoventilated alveoli) | • Cold exposure |
| - Impaired oxygen diffusion | • Redistribution of blood flow from extremities |
| • Anatomic shunts | |
| - Certain types of congenital heart disease | |
| - Pulmonary arteriovenous fistulas | |
| - Multiple small intrapulmonary shunts | |
| • Hemoglobin with low affinity for oxygen | |
| **Hemoglobin abnormalities** | |
| • ***Methemoglobinemia – hereditary, acquired*** | |
| • Sulfhemoglobinema – acquired | |
| • Carboxyhemoglobinemia (not true cyanosis) | |

**286. Answer is C (Congestive heart failure):** *Harrison 18th/p288 Harrisons 17th/231 Refer previous question*

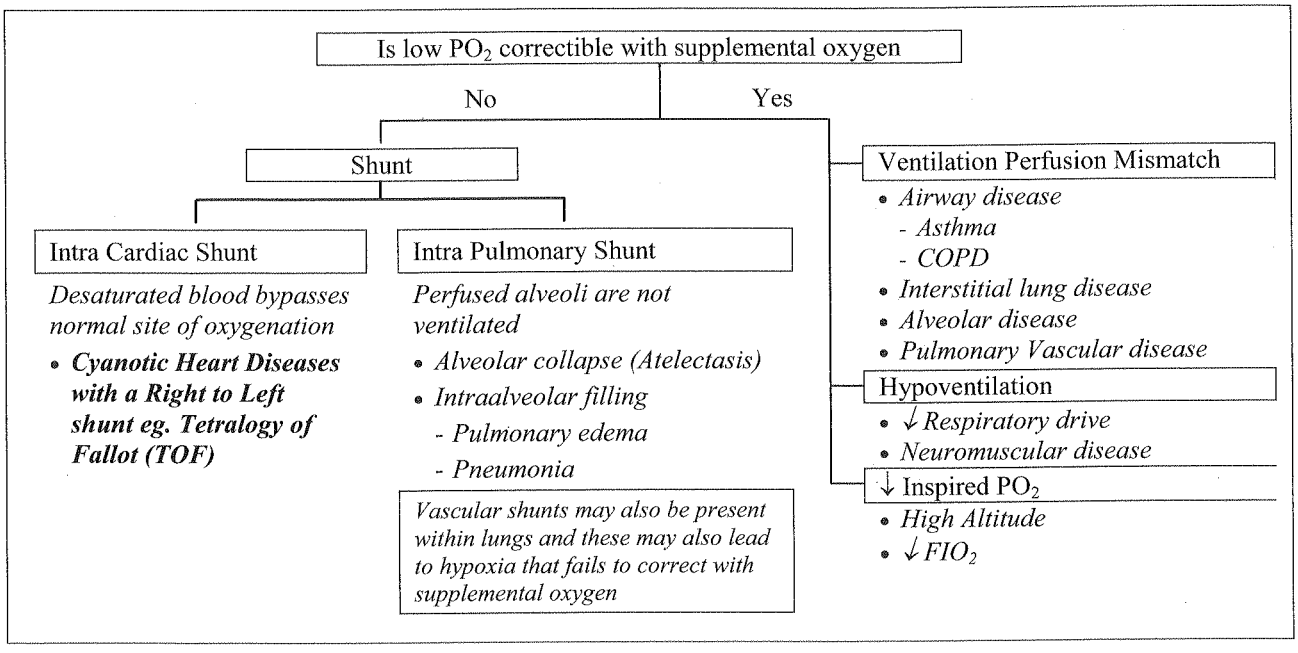
*Congestive Heart Failure is a cause for Peripheral cyanosis and not central cyanosis*

***Cyanosis when present in Asthma, pulmonic stenosis and alveolar hypoventilation is of the central type.***

**287. Answer is D (Tetralogy of Fallot (TOF):** *Harrisons 16th/1504; Harrisons 17th/1592; Nelsons 16th/1886*

*Presence of cyanosis that does not improve with supplemental oxygen suggest true pathological cardiac or pulmonary shunting of blood.*

***Presence of a cyanotic heart disease with an active right to left shunt (Tetralogy of Fallot) is a characteristic cause for failure of improvement with 100% oxygen supplementation. This occurs because desaturated blood in TOF shunts directly from the right (deoxygenated) side of the heart to the left side (systemic) of the heart by passing the lungs where oxygenation occurs.***




**288. Answer is B (Chronic bronchitis):** *Kumar Clarke 5th/ 845; Harrisons 16th/ 210; 17th/ 231; API 8th /348 Harrison 18th/p290*

Chronic bronchitis does not cause clubbing

| **Some causes of finger clubbing** | |
|---|---|
| **Respiratory** | **Cardiovascular** |
| Bronchial carcinoma, especially epidermoid (squamous cell) type (major cause) | Cyanotic heart disease |
| Chronic suppurative lung disese | Subacute infective endocarditis |
| **Bronchiectasis** | |
| Lung abscess | **Miscellaneous** |
| Empyema | Congenital – no disease Cirrhosis |
| Pulmonary fibrosis (e.g. cryptogenic fibrosing alveolitis) | Inflammatory bowel disease |
| Pleural and mediastinal tumours (e.g. mesothelioma) | **Primary billiary cirrhosis** |
| **Cryptogenic organizing pneumonia** | |

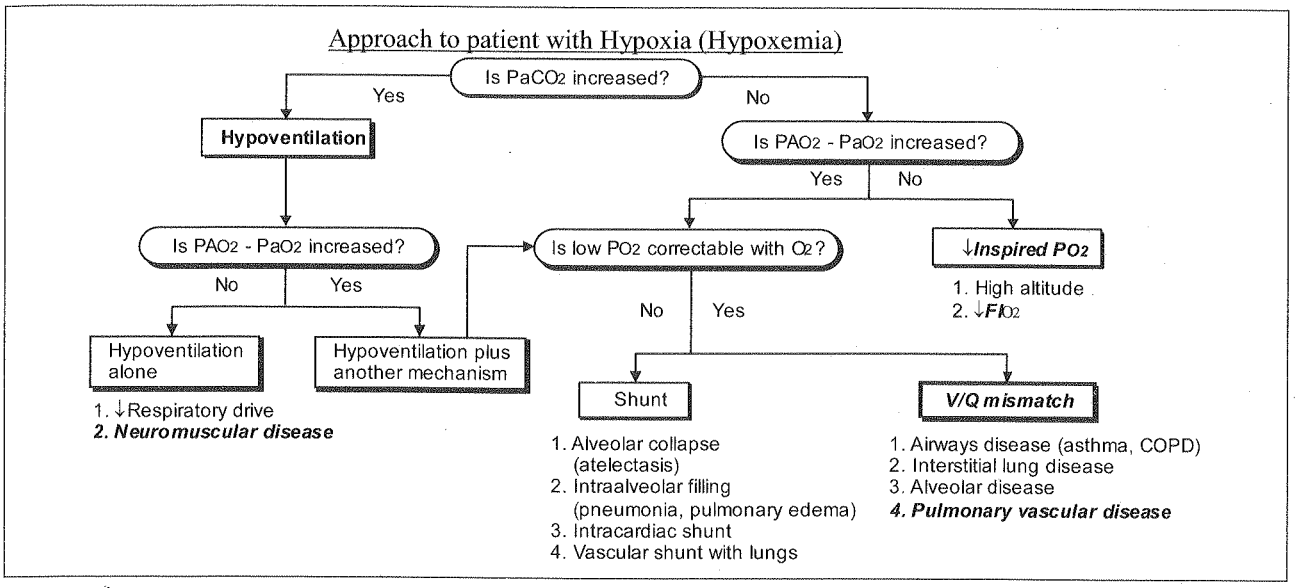
**289. Answer is A (Congenital Cyanotic Heart Disease) :** *Harrisons 17th/2982; Sapira's Art and Science of Bed side Diagnosis 3rd /159; PJ Mehta 15th/14; Physical Diagnosis : PreTest 6th/28 (Q-29)*

***Congenital cyanotic heart disease is a cause for bilateral clubbing***

| Causes of Unilateral Clubbing |
|---|
| • *Aneurysm of Aorta, innonimate artery, subclavian artery or axillary artery* |
| • *Brachial AV fistulas / malformations* |
| • *Infected arterial grafts* |
| • *Pancoast tumors* |
| • *Unilateral Erythromelalgia* |

**290. Answer is E (All of the above):** *Harrisons 17th/1591*

***The four basic mechanisms of hypoxemia are a decrease in inspired $PO_2$ (Decreased $FiO_2$), hypoventilation (as in Myaesthenia gravis), VQ mismatch (as in pulmonary emboli) and shunting.***




**291. Answer is A (Bilateral Diaphragmatic palsy):** *Harrisons Self Assessment & Board Review 17th/29; Sapira's Art and science of Bed side diagnosis 3rd /97; Platypnea Orthodeoxia syndrome: Review of Literature; South Med.Journal 97(7); 657-662*

***Bilateral diaphragmatic palsy is associated with orthopnea and not platypnea. It has not been mentioned as a cause for platypnea.***

*Severe COPD, pleural effusion and pulmonary embolism may present with either orthopnea or platypnea depending on the pathophysilogy.*
*Cirrhosis is an established cause for platypnea*

| Platypnea | Orthodeoxia |
|---|---|

Platypnea refers to an increase in dyspnea / breathlessness in the upright position
Orthodeoxia refers to decrease in oxygen saturation in the erect posture
*Platypnea is usually accompanied by orthodeoxia Platypnea-Orthodeoxia syndrome:*

**Causes of Platypnea – Orthodeoxia Syndrome**

**Pulmonary disease**

In any pulmonary disease that affects primarily the basal segments of the lungs, the assumption of an erect posture increases the ventilation perfusion mismatch and causes platypnea-orthodeoxia

**Various forms of severe pulmonary disease**
- Severe /Necrotizing Pneumonia
- Pleural effusions
- Basal Tuberculosis
- ARDS
- Severe parenchymal lung disease including interstial fibrosis and COPD (infrequently)
- Multiple Recurrent pulmonary emboli
- Post Pneumonectomy

AV malformations
- Congenital
- Cirrhosis
- Microvascular shunts due to hepatopulmonary syndrome

**Cardiac Disease**

Right to left intracardiac shunts
- ASD
- Patent foramen ovale
- Fenestrated atrial septal aneurysm

Right to left shunts in association with
- Pericardial effusion
- Constrictive pericarditis
- Eosinophlic endomyocardial disease

Clinical states associated with the platypnea –orthodeoxia syndrome -

| *Cardiac* | *Pulmonary disease* |
|---|---|
| • Patent foramen ovale | • ***Chronic obstructive pulmonary disease*** |
| • Atrial septal defect | • ***Pulmonary embolism*** |
| • Atrial septal aneurysm | • ***Pleural effusion*** |
| • Persistent eustachian valve | • Pulmonary emphysema |
| • Aortic aneurysm | • Pneumonectomy |
| • ***Pericardial effusion*** | • Lobectomy |
| • Constrictive pericarditis | • Severe/Necrotizing pneumonias - Staphylococcal pneumonea - Bibasilar pneumonia with pneumatocele |
| • Eosinophilic endomyocardial disease | • Acute respiratory distress syndrome |
| *Abdominal* | • Hepatopulmonary syndrme |
| • Hepatic cirrhosis | • Amiodarone toxicity |
| • Ileus | |
| *Miscellaneous* | |
| • Autonomic neuropathy | |
| • Kyphoscoliosis | |

**Footnote**

*Platypnea-orthodeoxia is a clinical syndrome characterized by dyspnea and deoxygenation accompanying a change to a sitting or standing position from a recumbent one. Two conditions must coexist to cause platypnea- orthodeoxia: An anatomic component in the form of an interatrial communication and a functional component that produces a deformity in the atrial septum and results in a redirection of shunt flow with the assumption of an upright posture. The anatomic defect can be an atrial septal defect, a patent foramen ovale, or a fenstrated atrial septal aneurysm. The functional component may be cardiac, such as pericardial effusion or constrictive pericarditis; pulmonary, such as emphysema, arteriovenous malformation, pneumonectomy, or amiodarone toxicity, abdominal, such as cirrhosis of the liver or illeus or vascular, such as aortic aneurysm.*

**292. Answer is A (Collapse of Right lung):** *Refer text below*

***Collapse of Right lung may present with homogeneous opacification of right hemithorax and ipsilateral mediastinal Shift.***

| Condition | | Findings |
|---|---|---|
| • *Consolidation* | : | *Ipsilateral Hamogenous opacification & No mediastinal shift* |
| • *Collapse* | : | *Ipsilateral Homogenous opacification & Ipsilateral mediastinal shift* |
| • *Hemothorax* | : | *Ipsilateral homogenous opacification & Contralateral shift* |
| • *Hydrothorax* | : | *Ipsilateral homogenous opacification & Contralateral shift* |

**293. Answer is C (Foreign Body Aspiration):** *O.P. Ghai Pediatrics 5th/ 340*

***Foreign Body Aspiration is an important cause of stridor in children. Obstruction leads to hyperinflation, chest wall hyperresonance and decreased breath sounds.***

*All the other choices mentioned in the question do not cause stridor.*

## Miscellaneous

**294. Answer is C (Pulmonary Embolism):** *Harrison's 17th/1584*

***Pulmonary Embolism is not associated with rhonchi***

**Rhonchi**

- Rhonchi are defined as *low pitched continuous sound's longer than 250 ms*
- These sounds are usually produced by presence of free liquid or mucus in the airways but may also be caused by vibration of larger airways at point of closure. They may also be produced by narrowing of lumen by foreign bodies or tumor

| Common causes of Rhonchi include: |
|---|
| • *Bronchial Asthma* |
| • *COPD – Chronic bronchitis, Bronchiectasis, Emphysema* |
| • *Cardiac Asthma (Pulmonary Edema)* |
| • *Foreign body* (Fixed monomorphic rhonchi - localized) |
| • *Tumor* (Fixed monomorrphic rhonchi – localized.) |

**295. Answer is E (Emphysema):** *Principles of Medical Physiology by Sircar 1st (2008)/320; Current Diagnosis & Treatment in Pulmonary Medicine 1st (2003)/5*

***Emphysema is associated with an increased static compliance but decreased dynamic compliance.***

***'The effect of emphysema on compliance is unique in that it results in an increase in static compliance but a decrease in dynamic compliance.***

*Static compliance increases due to destruction of elastic tissues in the alveolar walls. The reduction in elastic tissue makes it easier for the lung to expand in response to distending pressure, However the loss of elastic tissue in the walls of smaller airways makes them vulnerable to dynamic airway compression. This increases the airway resistance with consequent decrease in dynamic compliance - 'Principles of Medical physiology' by Sircar 1st (2008)/320*

**Compliance**

Compliance is a measure of 'distensibility' and is measured as a change in lung volume per unit change in pressure.

| Static Compliance | Dynamic Compliance |
|---|---|
| • Static compliance indicates compliance when the lungs are at rest<br>• Static compliance values reflect true lung compliance alone<br>• Static compliance reflects elasticity of the lung and is not affected by airway resistance because there is no flow | • Dynamic compliance indicates compliance when air flow is occurring<br>• Dynamic compliance values reflect lung compliance along with airway resistance<br>• Dynamic compliance is affected by both elasticity of the lung and airway resistance |
| Reduced static compliance indicates rigid lung tissue | Reduced Dynamic compliance (without change in static compliance) indicates ↑ed airway resistance |
| • Interstitial fibrosis (Fibrosing alveolitis)<br>• Atelectosis<br>• Pulmonary edema<br>• Pneumonia<br>• ARDS | • Obstruction<br>• Bronchospasm (Allergic Asthma)<br>• Collapse of small airways<br>etc |
| *Reduced static compliance is usually also associated with a decreased dynamic compliance due to associated airway resistance* | Reduced Dynamic compliance with reduced static compliance<br>*Most conditions where static compliance is reduced are also associated with reduced dynamic compliance due to associated increase in airway resistance* |
| Increased static compliance indicates easily expandible lung<br>• Emphysema<br>*Emphysema is associated with an increased static compliance but decreased dynamic compliance due to associated increased airway resistance.* | |

**296. Answer is B (COPD) :** *Ref. Text below; Harrison; Ganong*

***Pulmonary Compliance is increased in Emphysema (COPD)***

*Pulmonary Congestion, decreased surfactant and pulmonary fibrosis are all associated with reduced pulmonary Compliance.*

**Pulmonary Compliance**

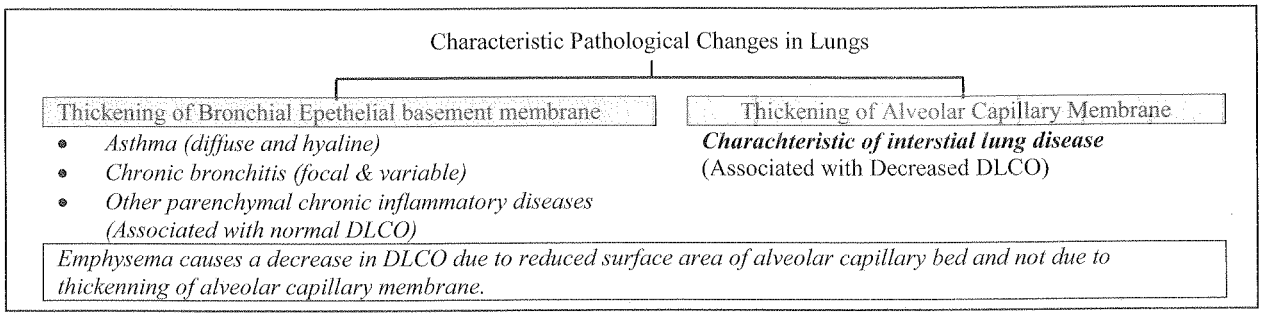
- Pulmonary Compliance expresses the distensibility (expansibility) of the lung and chest well
- *'Compliance'* refers to the change in lung volume (V) per unit change in trans pulmonary pressure

(*Compliance in inversely proportional to lung Elastance*)

| Decreased Lung Compliance | Increased Lung Compliance |
|---|---|
| Decreased lung compliance may be caused by conditions where lung is difficult to distend or surface tension is increased<br>• *Pulmonary fibrosis*<br>• *Atelectasis / pneumonia*<br>• *Pulmonary edema*<br>• *ARDS*<br>• *Pleural effusion / Empyema*<br>• *Pneumothorax*<br>• *Decreased surfactant (↑ surface tension)* | Increased compliance may be caused by loss of elastic recoil of lungs or decreased surface tension<br>• *Emphysema (COPD)*<br>• *Ageing*<br>• *Increased surfactant (↓ surface tension)* |

**297. Answer is C (Pulmonary fibrosis):** *Refer text below*

***Pulmonary Alveolar – capillary membrane thickening is a characteristic feature of interstitial lung disease like pulmonary fibrosis.***




**298. Answer is D (Bronchiolitis obliterans organizing pneumonia):** *Harrison 16th/1495*

***Bronchialitis obliterans organizing pneumonia has not been mentioned in association with smoking. All other options have been mentioned in relation to smoking in Harrison's text.***

*'**Even though chronic obstructive lung disease and neoplasia** are two most important respiratory complications of smoking, other respiratory disorders (spontaneous pneumothorax, **respiratory broncholitis**- interstitial lung disease, eosinophilic granuloma of the lung and pulmonary haemorrhage with Good pasture's syndrome) are also associated with smoking.' – Harrison 16th/1495*

Respiratory disease linked to Smoking

| Significant associations | Less significant associations |
|---|---|
| • **Chronic obstructive pulmonary disease**<br>- ***Emphysema***<br>- Chronic bronchitis<br>• **Lung cancer (Bronchial carcinoma)**<br>*Best documented associations is with squamous cell carcinoma, but may also be present with other histological subtypes **(eg. small cell)** (87% of lung carcinoma occur in active smokers those who have recently stopped smoking.)* | • Spontaneous pneumothorax<br>• Interstitial lung diseases<br>- ***Respiratory bronchilitis***<br>- DIP (Desquammative interstitial pneumonia)<br>- PLCH |

**299. Answer is B (Hamartoma):** *Sutton 7th/138,140,123; Harrisons 15th/1448*

***Hamartomas produce non cavitating popcorn calcifications.***
*Malignant lesions (squamous cell carcinoma) and granulomatous lesions (Wegener's granulomatosis, Caplan's syndrome) are established causes of cavitatory lesions.*

**300. Answer is B (Associated with pulmonary vasoconstriction) :** *Harrison 16th / 205; 17th/ 224 Harrison 18th/p 281*

***Although the mechanism of high altitude pulmonary edema remains obscure most studies suggest pulmonary vasoconstriction (venconstriction or arteriolar constriction) as the prime mechanism.***

**HAPE : High Altitude Pulmonary Edema**
This is a serious complication usually occruing at exposure to high altitude (>300m) in association with severe physical exercise and is classically seen in unacclametized healthy individuals.

**Pulmonary vasoconstriction has been suggested as the prime mechanism.**
*"Studies have been conflicting, some suggesting pulmonary venous constriction and other indicating pulmonary arteriolar constriction as the prime mechanism."- Harrison*

**May occur in both acclamatized and unacclamatized individuals**
"*Well recognized in unacclamatized yet otherwise healthy persons.*"

"***Acclamatized high altitude natives also develop this syndrome*** upon return to high altitude after a relatively brief sojourn at low altitudes." - *Harrison*

**HAPE is exacerbated by exercise and is associated with high cardiac output.**
*Increased cardiac output* and pulmonary arterial pressures with exercise combined with hypoxic pulmonary arteriolar constriction which is more prominent in young persons may combine to make this an example of prearteriolar high pressure pulmonary edema.

**301. Answer is B (Theophylline):** *Read text below*

*Theophylline relaxes the tone of bronchial smooth muscles, thereby causing bronchodilation*
*It may be used in the treatment of bronchial hyperplasia, it certainly does not contribute to bronchial hyperplasia.*

Smoking and other irritants cause the *hypertrophy of mucus glands*[Q] within the brochial wall, and contributes to narrowing of bronchioles by a variety of factors.

Prematurity *may be associated with bronchopulmonary dysplasia*[Q] *and bronchial hyperplasia*[Q]

**302. Answer is B (Direct spread from liver):** *Read below*

An *amoebic lung abscess is almost always secondary to spread from the liver.*

***Extraintestinal infection by E. histolytica most often involves the liver.*** Further involvement most commonly leads to Amoebic lung abscess.

*Infact pleuropulmonary involvement (Lung): is the most frequent complication of Amoebic liver abscess.*

**Remember:**

***Most common cause of a lung abscess is - 'Aspiration'.*** *However this holds true* ***for pyogenic (bacterial lung abscess)***

**303. Answer is A (Hydatid Cyst) :** ***Refer text below***

*Floating Water Lily Sign on Chest X-ray is characteristic sign of Pulmonary Cystic Echinococcosis or Pulmonary Hydatid Cyst.*

**Floating Water Lily Sign (Meniscus Sign; Sign of the camalote)**

- ***The floating water-lily sign is seen in hydatid infections when there is rupture or contained rupture of the Cyst.***
- When a cyst is ruptured, detachment of the endocyst membrane results in floating membranes within the pericyst that mimic the appearance of a water lily.
- This ***"Water-Lily"*** or ***"Meniscus" Sign*** denotes the entrance of air between the laminated membrane and the pericyst through a bronchiopericystic fistula and is observed as a thin, radiolucent crescent (*Cresecent sign*) in the upper part of the cyst on plain radiography.
- The sign is classically described on plain films (mainly chest X-ray) when the collapsed membranes are calcified but may be seen on ultrasound and CT-scan

| |
|---|
| The floating Water Lily Sign is also known as ***'Sign of the camalote'*** because of its resemblance to a water plant found floating upon the Amazon and other South American rivers |

**304. Answer is A (At end expiration):** *Schwartz Pre-Test / Q.20*

The changes in intrathoracic pressure that occur during different phases of respiration influence measurement of intravascular pressure. These changes are minimal at end expiration which therefore is the best phase for measurement of intravascular pressure.

**305. Answer is C (Cardiac tamponade):** *Harrison 14th/1336; 15th/1270, 1367; 16th/1319, 1416; 17th/ 1490, 1491 Harrison 18th/p 1972, 1973*

*Electrical alternans refers to a beat-to-beat alteration in one or more components of the ECG signal.*
***Total electrical alternans (P-QRS-T) with sinus tachycardia is a relatively specific sign for pericardial effusion, often with cardiac tamponade.*** *– Harrison 15th /1270*

| *Feature* | Cardiac Tamponade | Constrictive Pericarditis | Restrictive Cardiomyopathy | RVMI |
|---|---|---|---|---|
| Electrical Alternans | *May be present* | Absent | Absent | Absent |

Note: Pleural effusion and pneumothorax both are potential complications of carcinoma lung that present with respiratory distress but electrical alternans is not associated.

**306. Answer is C (Bradycardia):** *'Rudolph's Pediatrics" 21st/71; Fetal and Neonatal Neurology' 4th/493*

***The most common fetal response to acute hypoxia is Bradycardia***

*'The initial response of the normal fetus to acute hypoxia or asphyxia is bradycardia. Bradycardia results from chemoreceptor stimulation of vagal nerve' - Rudolph 21st/71*

**307. Answer is C > D (Immune complex > cell mediated) :** *Harrison 18th/p 2116 Harrison's 17th /1607;Rubin's Pathology 5th / 524,Robbins 7th / 739*

*Hypersensitivity pneumonitis is an immunologically mediated response to an extrinsic antigen that involves both immune complex (Type III) and cell mediated (Type IV) hypersensitivity reactions.*

***Classically however, Hypersensitivity pneumonitis was believed to be a immune complex (Type III) mediated hypersensitivity response which is therefore the better answer amongst the options provided.***

*However in strict terminology both option C and D should be correct.*

**Hypersensitivity Pneumonitis**

| Most patients have specific antibodies in there serum, which is a feature of (type III) immune complex hypersensitivity | Two third of patients have a non caseating granuloma which suggests the development of T cell mediated (Type IV) hypersensitiivity |
|---|---|
| *Classically described as Type III H.S* | *More recent evidence suggests associated cell mediated hypersensitivity* |

***Hypersensitivity Pneumonitis represents a combination of immune complex mediated (Type III) and cell mediated (Type IV) Hypersensitivity reactions***

*The exact contribution of each is debated*

**Note**

***Acute Hypersensitivity pneumonitis*** is a Type III immune complex mediated Hypersensitivity reaction

*(Clinical Anaesthesiology by 'Morgan' 4th / 970)*

**Types of Hypersensitivity Reactions: Review**

| Type I Hypersensitivity (IgE)Q | Type II Hypersensitivity (IgG & IgM)Q Cytotoxic, complement mediated lysisQ |
|---|---|
| *Includes:*<br>• Local: Eczema, Hay fever, Asthma (Atopy).Q<br>• Systemic: Anaphylaxis.<br><br>*Examples based on type I.H.S Q:*<br>• *Theoblad Smith phenomenon:Q This is anaphylaxis in guinea pigs.*<br>• *PK reaction (Prusnitz Kunster):Q Demonstrate that IgE is homocytotropic i.e. species specific.*<br>• *Casoni's test: Immediate type (IgE) H.S* | *Includes:*<br>• Complement mediated lysis.Q<br>• Antibody dependent cell mediated toxicity (formerly classified as type I).Q<br>• Changes in cellular function (former type V).Q<br>- Increased function: Grave's disease.Q<br>- Decreased function: M. Gravis.Q<br>• Phagocytosis.Q<br>*Examples includes:*<br>• *Those with Ag on RBC.*<br>*- Blood transfusion reaction.Q*<br>*- Hemolytic anemia e.g. with I.M. and mycoplasma.Q*<br>• *Those with Ag on Neutrophils: Agranulocytosis.Q*<br>• *Those with Ag on platelets: e.g. ITP.Q*<br>• *Those with Ag on basement membrane: Goodpasture's Q* |
| **Type III Immune complex (IgM & IgG)** | **Type IV Delayed hypersensitivity (cellular immunity)** |
| *Includes:*<br>• Local: Arthus reaction.Q<br>• Systemic: Serum sickness.Q<br>*Examples:*<br>• *Shick's test.Q*<br>• *Post streptococcal G.N.Q*<br>• *Detected by RAJI Assay.Q* | *Includes:*<br>• *Tuberculin test.Q*<br>• *Lepromin test.Q*<br>• *Contact dermatitis.Q*<br>• *Jones-Mote reaction (cutaneous basophilic hypersensitivity).Q*<br>• *Graft rejection (chronic).Q* |
| ***Hyprsensitivity Pneumonitis is associated with both Type III and Type IV Hypersensitivity*** | |

**308. Answer is B (Remove tube and Reattempt intubation):** *Lee synopsis of Anaesthesia 13th/215*

***The ideal next step is to confirm the position of ET tube and / or Remove the tube and reattempt intubation, if the tube is not in the trachea.As none of the options provided in the question can confirm the true position of the ET tube in the trachea the best course of action is to remove the tube and reattempt intubation.***

*The patient in question is presenting with characteristic features of left sided diaphragmatic hernia.*

*Incorrect placement of the tube into the esophagus (Esophageal intubation) will result in distension of stomach and bowel loops in the left hemithorax which would inturn shift the mediastinum and apical impulse to the right.*

***The apical cardiac impulse in this patient has been observed to shift further to the right after attempted ET intubation.This raises doubt about the correct positioning of ET tube in the trachea and suggests the possibility of improper placement of the ET tube into the esophagus.***

***The best next step in such a scenario is to confirm the position of ET tube.***

***None of the options provided in the question however allow us to confirm the position of the ET tube in the trachea***

***An X- ray chest cannot distinguish between tracheal and esophageal intubation and cannot confirm the position of the ET tube in the trachea. Hence option (A) can be excluded.***

A postero- anterior chest X-Ray (PA chest) can not confirm the position of tube in the trachea, as the oesophagus is situated immediately behind the trachea. A chest x-ray taken following intubation is done to confirm correct length of the tube rather than to find out whether it is sited in the trachea.

*Methods to confirm tracheal intubation*

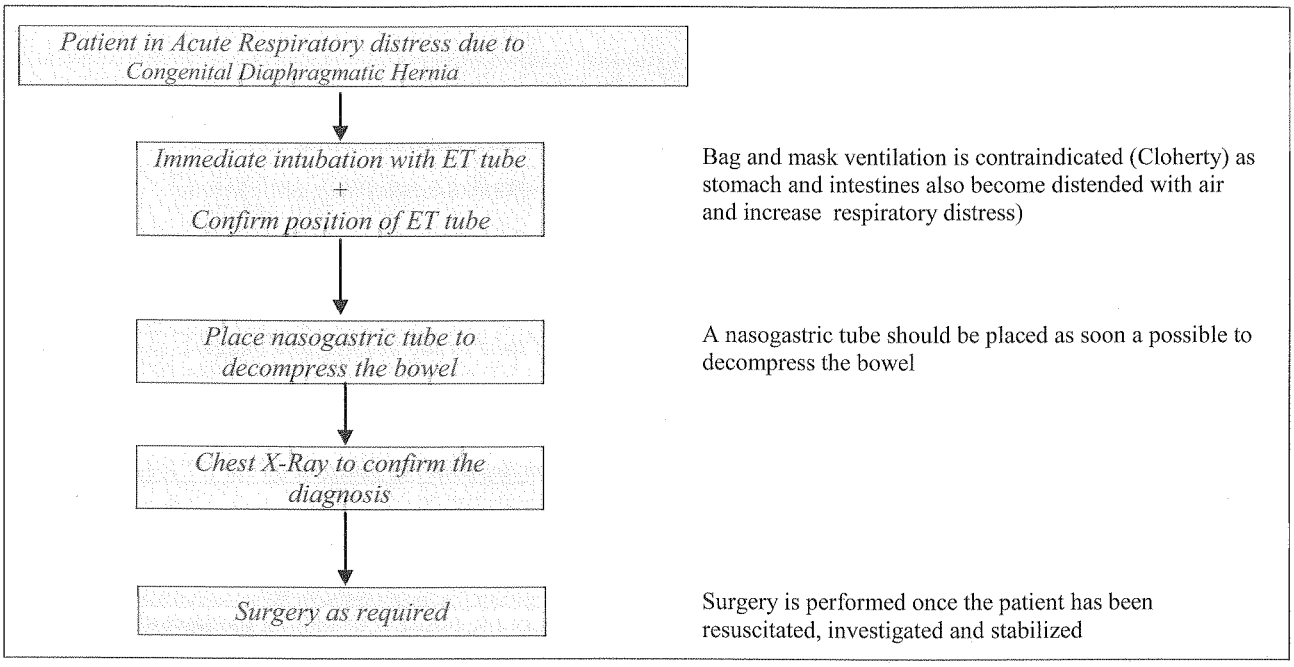
| *Tests which suggest tracheal placement (Not confirmatory)* | *Confirmatory tests* |
|---|---|
| • *Symmetrical bilateral chest movements when reservoir bag is squeezed*<br>• *Equal Breath sounds over lung fields when reservoir bag is squeezed*<br>• *Absence of gurgle over the epigastrium when reservoir bag is squeezed*<br>• *Misting of the tube (Water vaour deposition) during expiration*<br>• *Feeling of correct lung compliance and refilling of bag during expiration* | • *Capnography*<br>*Measures End tidal $CO_2$ in expired gas*<br>• *Esophageal detector device* |

***This leaves us still in doubt regarding the correct position of the ET tube and when in doubt, the best course of action is to remove the tube and reattempt intubation.***

*'When in doubt take it out'. It is easy to wrongly intubate the esophagus. This must be recognized immediately. If the clinical state of the patient deteriorates after intubation or if there is any doubt about tube placement, the tube should be removed' – Lee*

**309. Answer is C (Nasogastric tube insertion ) :** *Refer previous question*

***The ideal next step is to confirm the position of ET tube and / or Remove the tube and reattempt intubation, if the tube is not in the trachea. 'Removal of tube and reattempting intubation' is not provided amongst the option and position of the ET tube cannot be confirmed by chest X-ray. As both these possibilities are not provided in the list of options, the next best step is to decompress the bowel by nasogastric tube insertion and aspiration. This would help in relieving some respiratory distress and is therefore the single best answer of choice amongst the options provided.***
*X-Ray chest should be next step after nasogastric tube insertion to confirm the diagnosis, followed by surgery once the patient has been resuscitated, investigated and stabilized.*




**310. Answer is A (Bronchiolitis obliterans):** *Nelson 18th /1782.*

***The patient in question is presenting with charachteristic features of bronchiolitis obliterans.***

*Fever, cough, and wheeze are common clinical features of bronchiolitis obliterans and a period of initial improvement may well be seen in cases of bronchiolitis obliterans (Initial sign of B.O).*
*Hyperluscency or chest X-Ray and obstructive curve on pulmonary function tests furthur suggest the diagnosis of bronchiolitis obliterans.*

**Bronchiolitis Obliterans(BO)**

Bronchiolitis Obliterans is a chronic lung disease that results from obstruction of bronchii, bronchioles and smaller airways from fibrous tissue.

*Obstruction by fibrous tissue may be a sequelle to: (Etiology)*
- *Respiratory infections : Most common is Adenovirus*[Q] *(Rudolph)*
- *Inhalation of toxic gases*
- *Connective tissue disorders*
- Transplant recipients[Q]

**Clinical Features**

Initial Presentation

**Cough, fever** respiratory distress and **wheezing** followed by **initial improvement** may be the initial signs of BO –Nelson
*Presentation at this stage is similar to pneumonia, bronchitis, acute bronchiolitis*

Later Presentation

- **Prolonged wheeze (stridor)**
- *Chronic* **cough with sputum** *production*
- *Exercise intolerance (dyspnea)*

**Laboratory findings and imaging**
*(Suggest Features of Obstructive Lung disease)*

| | | |
|---|---|---|
| *Chest X-Ray* | : | **Hyperluscency** *and Patchy infiltrates* |
| *Pulmonary* | : | **Signs of airway obstruction (obstructive curve)** |
| *V-Q scan* | : | *Typical moth eaten appearance of multiple matched defects* |

**311. Answer is B (Strychnine):** *KDT 6th/454, 391; Encyclopedia of poisons and Antidotes 3rd/112*

***Strychnine is a CNS stimulant. It does not cause respiratory depression***

**Gelsemium causes Respiratory Depression**

***Gelsemium (ergot type alkaloid) is a CNS depressant.***
*'Symptoms of toxicity include difficulty in the use of voluntary muscles, muscle rigidity and weakness, dizziness, dry mouth, visual disturbances, tremor of extremities, sweating, conrulsions and* ***respiratory depression****. With large doses, paralysis and* ***death from respiratory failure can occur'*** *- 'The Encyclopedia of poisons and Antidotes' 3rd/112*

**Opium and Barbiturates are known to cause Respiratory Depression.**

*Barbiturates cause respiratory depression in high doses (KDT6th/391) (Barbiturates are CNS Depressants)*
*Opiates depress respiratory centre in a dose dependant manner (KDT 6th/454)*

**312. Answer is B (Acute physiology and chronic health evaluation)**

***APACHE*** *is a severity-of-disease classification system* ***and stands for*** *'**A**cute **P**hysiology and **C**hronic **H**ealth **E**valuation'.*

**313. Answer is A (Aspiration of gastric Contents)**

***Mendelson's syndrome is chemical pneumonitis caused by aspiration of gastric contents during anaesthesia.***

| *Mandelson Syndrome (Original Description)* |
|---|
| • Classic Mandelson Syndrome was described as a chemical pneumonitis from aspiration of gastric contents in obstetric cases while recovering from general anesthesia.<br>• A Triphasic Sequence was described in the original literature with<br>A. Immediate respiratory distress (with bronchospasm,cyanosis, tachycardia and dyspnea)<br>B. Partial Recovery<br>C. Gradual return to function<br>• The importance of 'gastric acid' was emphasized in the original description with a pH of less than 2.5 being required to cause chemical pneumonitis.<br>It has however been shown that the syndrome may well be caused by a pH of more than 2.5 by irritative action of alkaline aspirates or particulate matter *and gradual return to function is not the rule* |

**314. Answer is B (Palivizumab):** *Harrison 18th/ 1489; Pediatric Critical Care Study Guide: Text and Review (Springer) 2012/ 520*

***Palivizumab is a recombinant humanized, monoclonal IgG antibody directed against the RSV fusion protein.*** *It is licensed for the prevention of serious lower respiratory tract infection caused by RSV in children at high risk*

***Palivizumab*** should be administered intramuscularly as 15 mg/kg every 30 days for a total of five doses during RSV season, which is generally from November through March, to high risk infants. Infants or children that develop an RSV infection should continue to receive prophylaxis following recovery because the naturally acquired antibodies are not fully protective.

***Motavizumab*** *is a new, enhanced potency, humanized RSV monoclonal antibody that has demonstrated 50-100 times greater neutralizing activity against RSV. In completion of a phase III trial, Motavizumab was found equal to Palivizumab for the prevention of RSV hospitalization and superior to Palivizumab for reduction of RSV-specific outpatient medically attended lower respiratory tract infection*

**315. Answer is B (Bupropion):** *Cardiovascular Therapeutics: A Companion to Braunwald's Heart Disease (Elsevier Health Sciences, 2007)/194*

***Bupropion (along with Varenicline and Nicotine replacement therapy) is a USFDA approved first line agent for pharmacotherapy in Smoking Cessation.***

| USFDA Approved Agents for Smoking Cessation |
|---|
| • ***Nicotine Replacement Therapy*** (Transdermal Patch, gum, lozenges, oral inhaler, nasal spray) |
| • ***Bupropion*** (Atypical Antidepressant with dopaminergic and noradrenergic activity) |
| • ***Varenicline*** (Selective partial agonist at the Alpha4-Beta2 Nicotinic A-Choline receptor that is believed to mediate nicotine dependence) |

*Clonidine and Nortriptyline are two other medications that have efficacy but are NOT USFDA approved for this indication. These are classified as second line agents.*

# Kidney and Urinary Tract

# ESSENTIAL REVISION NOTES

## Urinary casts

**Urinary casts** are formed when proteins and other organic matter solidify in the renal tubule. The presence of casts in urine is indicative of disease of the nephron.

**Casts may contain:**

| *Proteins* | *Erythrocytes* | *Leucocytes* | *Epethelial cells* |
|---|---|---|---|
| Hyaline casts | Red cell casts | WBC cast | Epithelial casts |

### Clinical significance of different casts:

| | |
|---|---|
| a. ***Hyaline casts*** : | • This is a *normal constituent* [Q] of urine and has *no attached significance* [Q].<br>• *Tom Horsfall protein* [Q] is protein *secreted by epithelial cells of loop of henle* [Q].<br>• *This protein may be excreted as Hyaline cast.* [Q] |
| b. ***RBC cast*** : | • Are suggestive of *glomerular injury* [Q]. |
| c. ***White cell casts*** : | • Are suggestive of *interstitial injury* and may be seen in *interstitial nephritis* [Q] *WBC cast with bacteria indicate pyelonephritis* [Q]. |
| d. ***Broad granular casts*** : | • Are *seen in CRF* [Q] and suggests interstitial fibrosis and dilatation of tubules. |
| e. ***Pigmented muddy brown granular casts*** : | • Are suggestive of *ischaemic or nephrotoxic injury* [Q] i.e. *Tubular Necrosis* [Q]. |

***Presence of $\beta_2$ microgloobulin*** *in urine indicates tubular injury and not glomerular injury.*

**Tomm Harsfall Protein in urine is a feature of tubular proteinuria**

*Tomm Harsfall protein is synthesized in the tubular cells of ascending limb of loop of henle and distal tubule and is secreted into urine. Under conditions of tubulo interstitial injury (tubular proteinuria) increased Tomm Harsfall protein may be secreted in urine from injured tubular cells.*

**Glomerular proteinuria is associated with an increase Albumin: β2 microglobulin, ratio usually > 1000:1**

| Feature | Normal value | Glomerular proteinuria | Tubular proteinuria |
|---|---|---|---|
| Albumin: β2 microglobulin ratio | Usually 50:1 to 200:1 | Usually >1000 : 1 | Usually < 10:1 |

## Colour and Appearance of Urine

**Red Urine**
- *Beet ingestion (Betacyanin excretion)*
- *Phenolpthaline (in Laxatives)*
- *Vegetable dye ingestion*
- *Myoglobinuria*
- *Haemoglobinuria*
- *Seoratia Marcescens bacteria can cause the Red diaper' syndrome*

**Reddish Brown / Brown**
- ***Nitrofurantoin*** *(Brown)*
- *L-Dopa*
- *Alpha Methyl Dopa*
- *Metronidazole*

**Orange /yellow orange**
- ***Rifampicin*** *(yellow orange)*
- ***Pyridium*** *(orange) (Phenazopyridine)*

## Renal Function Tests

**Renal Function Test**

**Estimation of Glomerular Function**
- ***Creatinine Clearance Tests*** [Q]
- ***Inulin Clearance test*** [Q] *(used to assess Glomerular Filtration Rate- GFR)*

**Estimation of tubular function**
- ***Water Deprivation Test*** *(used to assess Distal Tubular Function)*

**Estimation of Renal Blood Flow/ Renal Plasma Flow**
- ***Paraaminohippurate (PAH) clearance*** *(used to assess Renal Plasma Flow -RPF)*

# Renal Failure & Tubulointerstitial Diseases

## Urine Diagnostic Indices: Differentiation of Prerenal and Intrinsic Renal failure.

*Acute tubular necrosis is a cause of Intrinsic ARF.* Q

**Differentiating features between Pre-renal and Intrinsic ARF**

- Prerenal Azotemia is the most common form of ARF and is caused by renal hypoperfusion either from generalized hypovolemia or from altered renal hemodynamics resulting in hypoperfusion
- ***By definition Renal parenchymal tissue is not damaged in prerenal ARF and prerenal ARF is rapidly reversible upon correction of the primary hemodynamic abnormality***
- Analysis of urine and blood biochemistry provides several useful 'Renal failure Indices' to distinguish prerenal ARF from intrinsic ARF (Ischemic /Nephrotoxic ARF)

**Urine Diagnostic Indices: Differentiation of Prerenal and Intrinsic Renal failure.**

| Diagnostic index | Prerenal ARF | Intrinsic renal ARF |
|---|---|---|
| Fractional Excretion of Na Q (%) | <1 | >1 |
| Urine Sodium Concentration (mmol/L) Q | <10 mmol/L | >20 mmol/L |
| Urine Sodium concentration (meq/L) Q | < 20meq/L | > 40 meq/L Q |
| Urine Creatinine To Plasma Creatinine ratio Q | >40 | <20 |
| Urine specific gravity Q | >1.020 | ~1.010 |
| Urine osmolality Q (mosmol/kg $H_2O$) | > 500 | < 350 |
| Renal failure Index Q $U_{Na}/(U_{CR}/P_{CR})$ | <1 | >1 |
| Urine urea Nitrogen to plasma urea Nitrogen Q | > 8 | <3 |
| Plasma BUN/Creatinine Ratio Q | >20 | <10-15 |
| Urinary sediment Q | Hyaline Casts | Muddy Brown Granular Cast |

# Renal papillary Necrosis

## Renal Papillary Necrosis

- Renal papillary necrosis is typically caused by ischaemic necrosis and sloughing of Renal Papllae (The papillary tip is the apex of renal pyramid)
- It is clinically charachterized by
  - *Loin Pain*
  - *Hematuria*
  - *Variable degree of renal impairment*

## Etiology / Predisposing factors

- ***Diabetes and analgesic abuse (NSAIDS) are the most common predisposing factors***
- The Acronym POST CARD is traditionally used to enlist the causes of papillary necrosis but it does not put the causes in a useful order of incidence

| | |
|---|---|
| P | Pyelonephritis |
| O | Obstruction |
| S | Sickle –cell disease |
| T | Tuberculosis |
| C | Cirrhosis |
| A | Analgesic abuse/Alcohol |
| R | Renal vein thrombosis |
| D | Diabetes |

POSTCARD – causes of papillary necrosis

## Stages of Acute Renal Failure (ARF)

| Phase of Renal Failure | Approximate onset and Duration |
|---|---|
| **Initiation Phase** | • *Begins with the onset of renal insult*<br>• *Lasts hours to days (usually less than 48hrs or 2 days)*<br>• *Reflects the time from the onset of the precipitating event (e.g., ischemic phase of pre-renal failure or toxin exposure until tubular injury occurs)* |
| **Maintenance phase (Oliguric Phase)** | • *Begins after the Initiation Phase once the renal injury becomes established*<br>• *Typically begins within 48 hours of the initiation phase and lasts for 10 to 14 days (May last longer)*<br>• *During this phase the GFR and Urine output progressively decrease until they stabilize at their lowest. (GFR is may be as low as 5-10ml/min and urine output is typically <400ml/day)*<br>• *Fluid retention gives rise to edema, water intoxication, and pulmonary congestion if the period of oliguria is prolonged (Hypertension frequently develops during this phase)*<br>• *Uremic (neurologic, gastrointestinal, and cardiovascular) complications may develop during this phase*<br>• ***Azotemia (Raised BUN and Creatinine) and Electrolyte imbalance typically arise during this phase.***<br>• ***Continuous Renal Replacement Therapy (CRRT) or Dialysis should be initiated in this phase.***<br>• *The oliguric-anuric phase generally lasts 10 to 14 days but can last for several more.*<br>• *The longer the patient remains in this phase, the poorer the prognosis for a return to normal renal function* |
| **Diuretic Phase** | • *Begins after the Oliguric phase and often precedes the recovery phase*<br>• *Typically begins 12 to 14 days after the initiation phase and lasts for about 10 days (May last longer)*<br>• *Nephrons do not concentrate urine sufficiently to conserve electrolytes and water*<br>• *Loss of concentration ability leads to a gradual increase in urine output from 1-3liters or more per day up to 5-6 litres per day.*<br>• *Risk of dehydration and death are high*<br>• *BUN and serum creatinine, potassium, and phosphate levels may remain elevated or continue to rise even though urine output is increased in some cases* |
| **Recovery Phase** | • *Begins after the Diuretic Phase (Roughly 24 days after the initiation phase)*<br>• *The recovery phase is the period during which repair of renal tissue takes place.*<br>• *Renal tubular function is progressively restored with improvement in concentrating ability.*<br>• *Its onset usually is heralded by a gradual return of urine output towards normal and a fall in serum creatinine, indicating that the nephrons are recovering*<br>• *The BUN and creatinine eventually returns to normal* |

Note: *According to the more recent classification systems the Diuretic Phase is included within the Recovery phase. The diuretic phase is recognized as an event that often complicates the Recovery Phase*

## Stages of Chronic Renal Failure (CRF)

| Pathological Stage | % Reduction in GFR | Comments |
|---|---|---|
| ***Diminished Renal Reserve*** | ***50 -80*** ***(Percent of normal)*** | • *The GFR is about 50% of normal.*<br>• *Serum BUN and creatinine values are normal*<br>• *Patients are asymptomatic.*<br>*(However, they are more susceptible to developing azotemia with an additional renal insult)* |
| ***Renal Insufficiency*** | ***20 to 50*** ***(Percent of normal)*** | • *The GFR is 20% to 50% of normal.*<br>• *Azotemia appears, usually associated with anemia and hypertension, Polyuria and nocturia can occur as a result of decreased concentrating ability.*<br>• *Signs and symptoms of renal failure first appear during this stage*<br>• *Sudden stress (e.g. with nephrotoxins) may precipitate uremia.* |
| ***Chronic Renal Failure (CRF)*** | ***Less than 20*** ***(Percent of normal)*** | • *The GFR is less than 20% of normal.*<br>• *The kidneys cannot regulate volume and solute composition*<br>• *Patients develop edema, metabolic acidosis, and hyperkalemia.*<br>• *Overt symptoms of renal failure typically appear during this stage*<br>*Overt uremia may ensue, with neurologic, gastrointestinal, and cardiovascular complications.* |
| ***End-Stage-Renal Disease (ESRD)*** | ***Less than 5*** ***(Percent of normal)*** | • *The GFR is less than 5% of normal;*<br>• *This is the terminal stage of uremia.* |

## Electrolyte Disturbaces in Uremia

| **Electrolyte disturbances in Uremia:** - *Harrison* |
|---|
| *Hyponatremia (Hypernatremia may also be seen)* |
| *Hyperkalemia (Hypokalemia may also be seen)* |
| *Hyperphosphatemia* |
| *Hypocalcemia* |
| *Hyperuricemia* |

## Management of Hyperkalemia

Management of Hyperkalemia

### First step

Stabilize Myocardium

| Method | Onset of action |
|---|---|
| Calcium gluconate or Calcium chloride | 3 to 5 minutes (effect begins within minutes and is marked by Improvement in ECG appearance) |

### Second Step

Reduce serum $K^+$ levels by shifting $K^+$ from extracellular to intracellular fluid

| Method | Onset of action |
|---|---|
| Insulin (Glucose) | Within 15 minutes *This is the fastest method* |
| Beta agonists (Albuterol) | In about 30 minutes |
| Sodium bicarbonate | At least 3-4 hours |

### Third step

Remove excess potassium from the body

| Method | Comment |
|---|---|
| Diuretics | Works only if patient has adequate kidney function |
| Resin exchangers (Kayexalate) (sodium polystyrene sulfonate) | • Slow acting (Requires 1-2 hrs before plasma $K^+$ decreases)<br>• Removes $K^+$ from blood into gut in exchange for an equal amount of $Na^+$. |
| Hemodialysis | Definitive treatment of choice in patients with advanced renal failure and severe hyperkalemia |

## Advanced Life Support Guidelines for Treatment of Hyperkalemia

**Advanced Life Support Guidelines for Treatment of Hyperkalemia**

| **Mild elevation (5.5-6 mmol/L)** | **Moderate / severe elevation without ECG changes (>6 mmol/l)** | **Moderate / severe elevation With toxic ECG changes (>6 mmol/l)** |
|---|---|---|
| Remove K+ from body<br>▪ Cation exchange resins<br>▪ Diuretics<br>▪ Consider dialysis | Remove K+ from body<br>▪ Dextrose / insulin infusion ( +/-)<br>▪ Nebulized salbutamol<br>▪ Intravenous NaHCO3 (+)<br>▪ strategies as for mild elevation | First stabilize the heart / Antagonize the toxic effects of Hyperkalemia.<br>Calcium gluconate (+)<br>Other strategies |

## Glomerular Diseases

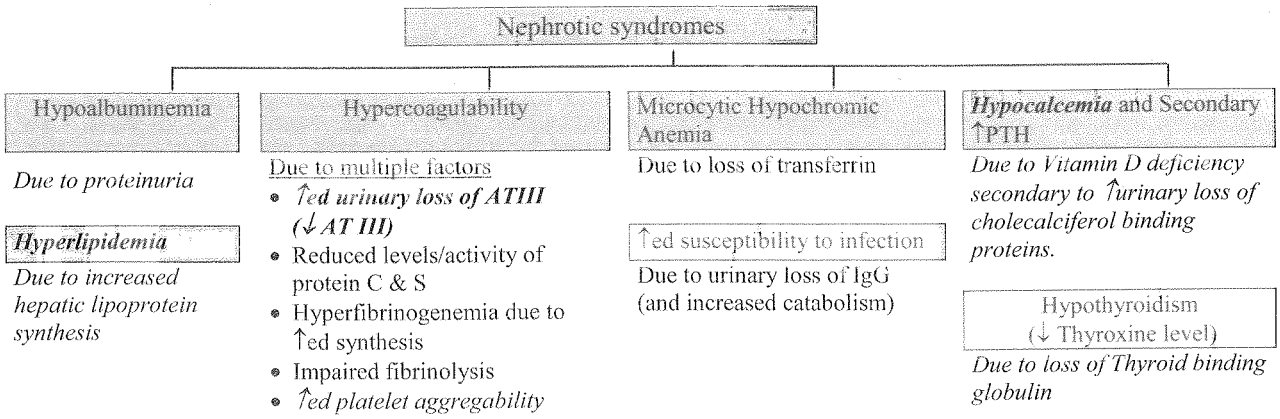
# Nephrotic Syndrome

**'Essentials' in the diagnosis of nephrotic syndrome:**

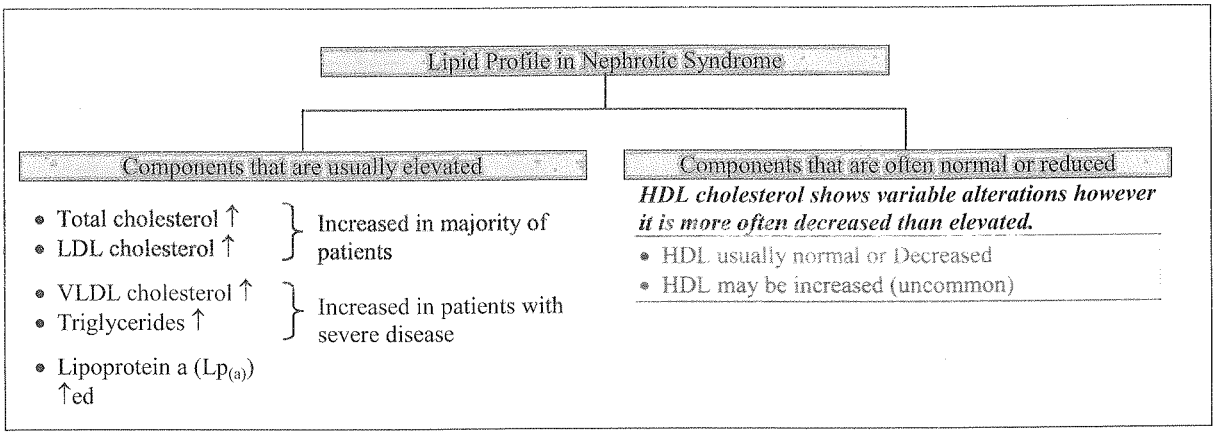
| 'Essentials' in the diagnosis of nephrotic syndrome : |
|---|
| 1. Proteinuria : excretion > 3.5g/1.73 m2 per 24 hrs. Q |
| 2. Hypoalbunemia : albumin < 3g/dl. Q |
| 3. Peripheral edema. Q |

*Hyperlipidemia Q occurs in 50% of those with early nephrotic syndrome and is much more common in patients who excrete larger amounts of protein per day.*

## Features of Nephrotic Syndrome




## Lipid Profile in Nephrotic Syndrome



# Minimal Change Disease

## Minimal Change Disease

- Most common cause of Nephrotic syndrome in children (80% in children; 20% in adults)
- Peak Age of onset is between 6-8 years of Age (usually < 10 years)
- Type of onset : Insiduous

## Clinical features

- Peripheral Edema: Presenting Feature

Nephrotic syndrome is the typical presentation
Peripheral edema is the hallmark of Nephrotic syndrome occurring when serum albumin levels become less than 3g/dl
Initially dependent Edema $\xrightarrow{Later}$ Generalized edema
May develop Pleural effusion, pulmonary edema, ascitis

- Hematuria : 20-30%
- Hypertension : V. Rare
- Renal failure : Does not usually progress to renal failure

## Laboratory (Features of Nephrotic syndrome)

- *Proteinuria*
- *Hypoalbuminemia*
- *Hyperlipidemia/Hyper cholesterolemia (Increased hepatic prduction of lipids)*
- *Hypercoagulability*

## Renal pathology (Biopsy)

| Investigation | Observation |
|---|---|
| Light microscopy Q | No abnormality hence the term minimal change |
| Electron microscopy Q | Fusion of foot processes |
| Immunofluorescence Q | Absence of immunoglobulin or complement |

## Prognosis

- *Prognosis is Good*
- *Response to steroids is Excellent*
- *Does not progress to Renal Failure*

## Treatments

- *Corticosteroids form the mainstay for treatment of MCD*

## Nephritic Syndrome and Rapidly Progressive Glomerulonephritis (RPGN)

**Syndrome of acute nephritis or nephritic syndrome**

| Acute Nephritic Syndrome |
|---|
| *Hypertension Q* |
| *Hematuria with RBC cast in urine Q* |
| *Oliguria Q* |
| *Pyuria Q* |
| *Azotemia Q* |
| *Mild to moderate proteinuria Q* |
| *Edema Q* |

*The syndrome of acute nephritis or nephritic syndrome characterizes acute Glomerulonephritis clinically.*

*Patients with Acute nephritis syndrome also commonly have proteinuria and edema but these are not as severe as those encountered in nephrotic syndrome.*

# Rapidly Progressive Glomerulonephritis (RPGN) or Crescenteric Glomerulonephritis

## Types of Crescenteric Glomerulonephritis (RPGN)

**Types of Crescenteric Glomerulonephritis (RPGN)**

**Type I RPGN (Anti – GBM Antibody)**
- **Idiopathic Anti Glomerular Basement membrane disease**
- Good pasture's Syndrome

**Type II RPGN (Immune Complex)**
- Idiopathic
- **Acute Post Streptococcal Glomerulonephritis (PSGN)**
- Lupus Glomerulonephritis (SLE)
- **Henoch Schonlein Purpura (HSP)**
- IgA Nephropathy
- Membranoproliferative Glomerulonephritis (Harrisons 17th / 1785)
- Cryoglobulinemia (Harrision 17th/ 1785)
- Post infectious (After subacute Bacterial Endocarditis) Glomerulonephritis

**Type III RPGN (Pauci – immune)**
*ANCA – Small Vessel Vasculitis*
- Wegener's granulomatosis
- Microscopic polyangitis
- Churg – Strauss syndrome

## Features of RPGN

**RPGN is characterized by a Subacute glomerular inflammation with:**
- *Nephritic urinary sediment, i.e. RBC casts, WBC casts*
- *Sub-**nephrotic non-selective proteinuria*** (proteinuria < 3.5 g/24 hr) *(selective proteinuria is a feature of minimal change disease)*
- *Oliguria and Edema*
- *Hypertension*
- *Presence **of crescents** pathologically*

## Differential Diagnosis of Glomerulonephritis based on Proliferative changes

**Proliferative changes in Glomerulonephritis** *(Refer: Chandrsoma Taylor 3rd /702, 708)*

- *Glomerulus contains Endothelial cells, Epethelial cells, and Mesangial cells. Any of the three cell types may undergo proliferation in different types of Proliferativ Glomerulonephritis.*
- *Proliferative changes are not limited to Membranoproliferative and Mesangioproliferative Glomerulonephritis, but may be seen in several other forms of Glomerulonephritis*

**Glomerulonephritis and Proliferative changes**

**Glomerulonephritis without proliferative changes**

| *Glomerulonephritis* | *Proliferative changes* |
|---|---|
| *Minimal change Disease* | *- (Absent)* |
| **Membranous Glomerulonephritis** | *- (Absent)* |
| *Diabetic Nephropathy* | *- (Absent)* |
| **Amyloidosis** | *- (Absent)* |
| **Focal segmental Glomerulosclerosis** | ± Variants with proliferative lesions have been described including cellular lesions with endocapillary hypercellularity- (Harrisons) |

**Glomerulonephritis with proliferative changes**

| *Glomerulonephritis* | *Proliferative changes* |
|---|---|
| *Post streptococcal GN* | *+ (Crescents)* |
| *Antibasement membrane disease (Good – pasture's syndrome)* | *+ (Crescents)* |
| *IgA Nephropathy (Berger's)* | *+ (Mesangial)* |
| *Henoch Schonlein Purpura* | *+ (Mesangial)* |
| *Mesangioproliferative GN* | *+ (Mesangial)* |
| *Membranoproliferative GN* **(Mesangiocapillary GN)** | *+ (Endothelial & Mesangial)* |
| *Focal Glomerulonephritis* | *+ (Focal)* |
| *Secondary Glomerulonephritis SLE / PAN* | *+ Variable* |

Note : Crescents represent proliferation of epethelial cells

## Differential diagnosis of Nephritic syndromes based on complement levels

| *Low complement levels* | *Normal complement levels* |
|---|---|
| ***(Immune complex glonerulonephritis)*** | • ***Anti GBM disease:*** *Good posture's syndrome* |
| • *Idiopathic proliferative glomerulonephritis* | • ***Pauci*** *immune* ***glomenulonephritis*** |
| • *Crescentric glomenelonephritis* | - *Wegeners granulomatoses* |
| • *Membranoproliferative glomerulonephritis* | - *Microscopic polyarteritis nodosa* |
| • *Lupus nephritis* | • *Immune* ***complex mediated*** |
| • *Cryoglobulinemia* | - *IgA Nephropathy* |
| • *Bacterial endocarditis* | - *Henoch schonlein purpura* |
| • *Shunt nephritis* | - *Fibrillary Glomerulonephritis* |
| • *Post infectious glomerulonephritis (post streptococcal)* | |

## Recurrent episodes of gross haematuria

*Recurrent Gross Haematuria should be distinguished from isolated episodes of gross hematuria, as it is a charachteristic feature of some specific disorders*

| *Charachteristic Causes of Recurrent Gross Haematuria (Nelson 18th/2169)* | |
|---|---|
| *1. IgA Nephropathy*<br>*2. Alports syndrome*<br>*3. Thin Glomerular basement membrane disease*<br>*4. Hypercalciuria*<br>*5. Urolithiasis* | *Isolated Glomerular diseases with recurrent Gross haematuria* |

## Hematuria following Respiratory Tract Infection: Approach

**Hematuria following Respiratory Tract Infection**

**Synpharyngitic Hematuria**

Hematuria develops early after pharyngitis (< 1week) without any significant latent phase after pharyngitis

- Primary Renal Manifestations
  - IgA Nephropathy
    - *Recurrence may occur*$^{Q}$
    - *C3 levels are usually normal*$^{Q}$
    - *ASO titres are usually normal*$^{Q}$

**Delayed hematuria**

Hematuria develops after pharyngitis after a delay (> 1 week) with a significant latent phase after pharyngitis

- Systemic Manifestations along with Renal manifestation
  - Skin (Rash/Purpura)
  - Arthralgia
  - Abdominal pain
  - Nephritis
  - H.S. Purpura
    - *Recurrence may occur*$^{Q}$
    - *C3 levels are usually normal* $^{Q}$
    - *ASO titres are usually normal* $^{Q}$

**Note**

*Nephritis in HSP almost always appears after the development of skin manifestations-Rash/Purpura*$^{Q}$

- Primarily Renal Manifestions
  - Post Streptococcal GN (PSGN)
    - *Recurrence is rare*
    - *C3 levels are depressed*
    - *ASO titres are usually elevated.*

## Differentiating IgA Nephropathy from Post-streptococcal Glomeulonephritis

| IgA Nephropathy | Post streptococcal Glomerulonephritis |
|---|---|
| • **Synpharygitic Hematuria**<br>*Hematuria develops usually within 2-4 days of Pharyngitis /URTI*<br>*This is called synpharygitis hematuria since there is no significant latent period between development of hematuria and pharyngitis* | • Delayed Haematuria<br>Hematuria develops 1-3 weeks after pharyngitis /URTI<br>*This is called delayed Hematuria since there s a significant latent period between development of hematuria and pharyngitis* |
| • **Recurrence is common**<br>*'Hematuria occuring in IgA nephropathy typically lasts for several days and then subsides, only to return every few months'*<br>Recurrent Gross Hematuria | • Recurrence is rare<br>*'Complete Recovery occurs in more than 95% of patients with PSGN. One attack confers life long immunity and recurrences are extremely rare* |
| • **Serum complement C3 levels are Normal**<br>C3 levels Normal | • **Serum levels of complement C3 are reduced**<br>C3 levels depressed in > 90% |
| • **Antistreptolysin O titres are usually normal** | • **Antistreptotysin O titres are usually elevated**<br>*'Increased ASO titres are associated with Acute PSGN rather than IgA Nephropathy'* |

| Laboratory Feature of Renal vasculitis in children due to HSP | |
|---|---|
| • *Serum IgA levels* | *Elevated (60% of patients have an elevated serum IgA)* |
| • *Antinuclear Antibody (ANA)* | *Negative* |
| • *Antineutrophil cytoplasmic Antibodies (ANCA)* | *Negative* |
| • *Complement (C3, C4)* | *Normal (Even though immune complexes containing IgA are essential to the pathophysiology of HSP, serum complement levels are usually normal* |
| • *Cryoglobulins* | *Negative* |

## Berger's Disease/IgA Nephropathy

**Aetiopathogenesis**

*Respiratory or gastrointestinal exposure to environmental agents (viruses, bacteria etc.)*

↓

Genetic or acquired abnormality of immune regulation resulting in *increased mucosal IgA synthesis* Q

↓

Formation of circulating *IgA immune complexes* Q, which are entrapped *in mesangium.* Q

| Microscopic Pathology Q | Immunofluorescence | Electron Microscope |
|---|---|---|
| ***Mesangioproliferative*** *(diffuse) glomerulonephritis >* ***Segmental*** *proliferation confined to some glomeruli* ***(focal*** *proliferative glomerulonephritis)>* *Overt crescentric glomerulonephritis (rare)* | *Mesangial deposition of IgA often with C3 and properidin* Q *(IgG is present in 50% of cases)* Q | *Electron dense deposits in mesangium* Q. mesangial hypercellularity, sclerosis |

**Clinical**

***Haematuria :*** Most common presentation is with ***gross haematuria*** *24 to 48 hrs after a pharyngeal / gastrointestinal infection* Q / vaccination or strenuous exercise.

***Microscopic haematuria*** Q detected during routine physical examination may be the presentation.

***Proteinuria*** (Nephrotic syndrome) : *may or may not be present* Q *- Robbins*

***Hypertension*** (20-30%) is *unusual at presentation.* Q

# Goodpasture's Syndrome

## Good pasture's syndrome

Good pasture's syndrome is an autoimmune disease characterized by formation of Anti GBM antibodies that attack both pulmonary capillaries and the Glomerulus (GBM)

*Preceding Resp infection*
*Toxic lung exposure*
*Drug exposure Etc*

*Antibodies against Non collagenous Domain (NCL) of α3 chain of collagen type IV*
*(Found in Glomerular Bacement membrane & Pulmonary capillaries)*

Serology

- *Circulating Anti GBM antibodies (IgG): Positive*
- *ANCA antibodies: Typically Negative (May be present in upto 30% )*
- *ANA antibodies : usually normal*
- *C3 levels : Usually normal*

Two Age Groups

- *Young men in late 20's (Men >> females)*
- *Men and women their 60-70's*

Antibodies agonist Glomerular Basement Membrane (GBM)

Antibodies against pulmonary capillaries

Glomerulonephritis /Renal Disease

- Features of Acute Glomerulonephritis (RPGN)
  *Hematuria*[Q]
  *Proteinuria*[Q]
  Edema
  *Rapidly progressive renal failure*[Q]
- Pathological Picture[Q]
  *Diffuse crescenteric Glomerulonephritis*[Q]
  *Linear IgG*[Q] *staining along basement membrane on immunofluorescence*[Q]

*Dysmorphic RBC and RBC cast are present in urine suggesting Glomerulonephritis*[Q]

Pulmonary /Lung Manifestations

Clinical

- Hemoptysis (Frank)
  *Hemoptysis is largely confined to smokers*
- Dyspnea

X-Ray finding[Q]

- *Diffuse bilateral pulmonary infiltrates*[Q]

## Goodpasture's syndrome and ANCA

*ANCA is typically negative in Goodpastures syndrome and it is classified as an ANCA negative vasculitis*
*Nevertheless*
*ANCA seropositivity may occur in upto 30 percent of patients with Goodpasture's syndrome.These patients with ANCA have subtle signs of a systemic vasculitis and represent an overlap between goodpastures and either Wegener's granulomatosis (WG) or Microscopic polyangitis(MPA)-Current Diagnosis and Treatment in Pulmonary Medicine 1st (2003)/211*

Triad of Goodpasture's syndrome (*Ferri's Color Atlas & Text of Clinical Medicine*)

- *Glomerulonephritis*[Q] *(RPGN; crescents)*
- *Pulmonary Haemorrhage*[Q] *(Diffuse Alveolar Haemorrhage)*
- *Antibodies to basement membrane antigens*[Q] *(Anti-GBM antibodies)*

# Alport's Syndrome

## Alport's Syndrome

Alport's syndrome is an inherited disorder charachterized by hereditary nephritis, senserineural deafness and ocular abnormalities.

*Alport's syndrome is the most common hereditary nephritis*[Q]

## Genetic defect, Pathology

- Primary pathology in Alport's syndrome is an abnormality in type IV collagen
  (Type IV collagen is the predominant collagen in basement membrane)
- ***The most common form of Alport's syndrome is due to mutation of the COLA4A5 ( $\alpha - 5$ Chain) gene located on the X chromosome***[Q]***.***
- The most common inheritance pattern for Alport's syndrome is X Linked – *Classic Alport's syndrome*
  *Alport's syndrome may be inherited as X-Linked, Autosomal recessive, or Autosomal dominant disorder but classic Alport's syndrome in inherited as an X linked disorder.*

## Clinical Triad

**Alport's Syndrome**

| Nephrosis / Kidney | Otological (Ears) Symptoms | Ocular (Eye) |
|---|---|---|
| • *Hematuria (Micro /Macro)*<br>• *Proteinuria*<br>• *Progressive* ***Renal Failure*** | • *Sensorineural hearing loss* (Labyrinthine hearing loss particularly in high frequency) | • ***Lenticonus*** is characteristic<br>• *Cataract (lens opacity)*<br>• *Corneal erosions*<br>• *Keratoconus*<br>*Myopia induced by Lenticonus & keratoconus* |

## Pathological Findings in kidney

- *Nephritis (Hematuria, Proteinuria, Progressive renal insufficiency)*
- *Sensorineural deafness*
- *Ocular abnormalities (Lenticonus > Recurrent corneal erosisons, corneal opacipies)*
- *Irregular thickening and thinning of Basement membrane*
- *GBM may appear normal or diffusely thin*
- *Splitting of Lamina and micro granulation's may be seen*

## Treatment and Prognosis

- *No specific treatment to slow the progress of this condition.*
- *Patients are good candidates for Renal transplantation.*
- *Recurrence of disease in renal transplant is rare.*

## Clinical Manifestation of Alport's Syndrome (Triad)

*Because it is inherited as an Xlinked disorder, women are usually less severely affected than men.*

Most common inheritance: X Linked (Recessive)
Most common defect : Alpha 5 chain of collagen IV

| Nephritis | Sensorineural Deafness | Ocular Abnormalities |
|---|---|---|
| • Hematuria is the classic presenting feature and occurs early in life<br>• Proteinuria often develops but its development is usually noticed years after hematuria is first observed (delayed)<br>• Chronic Renal Failure develops in most individuals and is often observed in late teens or early 20's | • Sensorineural deafness is the most common extrarenal manifestation in Alport's syndrome<br>• Primarily in the high tone range<br>• Frequently detectable only by an audiogram<br>• Usually not progressive (Harrison)<br>*According to Clinical Pediatric Nephrlogy, hearing loss is progressive* | • Anterior Lenticonus is charachteristic (often bilateral)<br>• Recurrent corneal erosisns and lens opacities are often associated<br>*Lenticonus together with hematuria is considered pathognomic of classic AS* |

# Diabetic Renal Disease

## Microalbuminuria and Diabetic Renal Disease

- *Microalbuminuria is the first clinically detectable sign of diabetic nephropathy*
- Microalbuminuria refers to excretion of albumin in the urine in amounts that are abnormal but below the limit of detection of conventional urine dipsticks[Q]

> *Microalbuminuria is defined as excretion of 30-300 mg of albumin/day in a 24 hour collection[Q] or 30-300µg/mg[Q] creatinine in a spot collection.*

- The presence of albumin in the urine in the range of microalbuminuria is *best determined by a urinary Albumin/Creatinine ratio in a spot voided urine (Prefered method for delecting microalbuminuria)[Q]*
- *Microalbuminuria is best detected by Sensitive Radioimmuneassays[Q]*
- The recognition of microalbuminuria in patients with diabetes mellitus allows identification of diabetic nephropathy and institution of treatment to reduce the risk of progressive kidney disease at an earlier stage than would be possible with conventional urine dip-sticks

> There is clear evidence that the detection of early diabetic nephropathy manifested by microalbuminuria is responsive to antihypertensive therapy in particular the use of ACE Inhibitors or Angiotensin Receptor Blockers.

**Stages of Diabetic Nephropathy according to Mogensen:**

| Stage | Duration of diabetes | Clinical, biological and pathological signs related to renal disease |
|---|---|---|
| 1 | At diagnosis | • *No clinical or biological signs of renal injury*<br>• *Hypertrophy of the kidneys*<br>• *Glomerular hyperfiltration* |
| 2 | 2-5 years | *Clinically and biologically 'silent' nephropathy* |
| 3 | 5-10 years | **Early nephropathy:**<br>• ***Microalbuminuria***<br>• *High blood pressure*<br>• *Normal GFR* |
| 4 | 10-20 years | **Established diabetic nephropathy:**<br>• ***Macroalbuminuria***<br>• *High blood pressure*<br>• *Decreasing GFR*<br>• *Pathology: mesangial expansion; GBM thickening; and glomerular sclerosis* |
| 5 | >20 years | **End-stage renal disease**<br>• *Pathology: advanced fibrosis of the kidneys*<br>Need for:<br>• *Renal transplant (± pancreas)*<br>• *Peritoneal dialysis*<br>• *Hemodialysis* |

**Glomerular Lesions in Diabetes**

| Diffuse glomerulosclerosis : | Nodular glomerulosclerosis |
|---|---|
| • Is the ***most common pattern of involvement***[Q]<br>• The most common pathological change is ***thickening of glomerular basement membrane***[Q] which occurs virtually in all diabetics and is part and parcel of diabetic microangiopathy<br>• Various exudative lesions such as capsular hyaline drops or 'fibrin caps' may be present<br>• ***Capsular drop***[Q]: is an eosinophilic thickening of parietal layer of Bowman's capsule and bulges into glomerular space<br>• ***Fibrin caps***[Q] : is a homogeneous eosinophilic material appearing on the wall of a peripheral capillary of a lobule | • Is virtually ***pathognomic***[Q] ***of diabetes mellitus***<br>• Is also called ***Kimmelstiel-Wilson lesion*** *or* ***Intercapillary glomerulosclerosis***[Q]<br>• The pathological change consist of one or more nodules in a few or many glomeruli<br>• Uninvolved lobules and glomeruli all show striking diffuse glomerulosclerosis |

**Capillary basement membrane thickening**

"The earliest morphological abnormality in diabetic nephropathy is thickening of basement membrane" (and expansion of mesangium due to accumulation of extracellular matrix)

## Glomerular Lesions in SLE (Wire Loop Lesions)

**Wire loop lesions:**

- Wire loop lesions represent local PAS – Positive thickening of glomerular capillary walls and are characteristically seen in Lupus Nephritis (SLE)
- These lesions result from subendothelial deposits between endothelium and basement membrane. When extensive and confluent, these subendothelial deposits create a homogenous thickening of the capillary wall which can be seen in light microscopy as 'Wire loop lesion'
- Wire loop lesions are most characteristic of Lupus Nephritis Class IV or Diffuse Lupus Nephritis
  These may however also be seen in Class III (Focal Lupus Nephritis) and Class V (membranous) Lupus Nephritis.

Wire Loop Lesion (Lupus Nephritis)

| Most characteristic of: | Also seen in: |
|---|---|
| ***Lupus Nephritis Class IV*** *(Diffuse Lupus Nephritis)* | *Lupus Nephritis Class III (Focal) >* *Lupus Nephritis Class V (Membranous)* |

## Glomerular Lesions in HIV

***The most charachteristic Glomerulopathy in HIV is focal segmental Glomerulosclerosis (FSGS), which typically reveals collapse of the glomerular capillary tuft called collapsing glomerulopathy***

## Hepatitis C infection and Glomerular lesions

**Three clinicopathologic glomerular syndromes associated with hepatitis C are:**

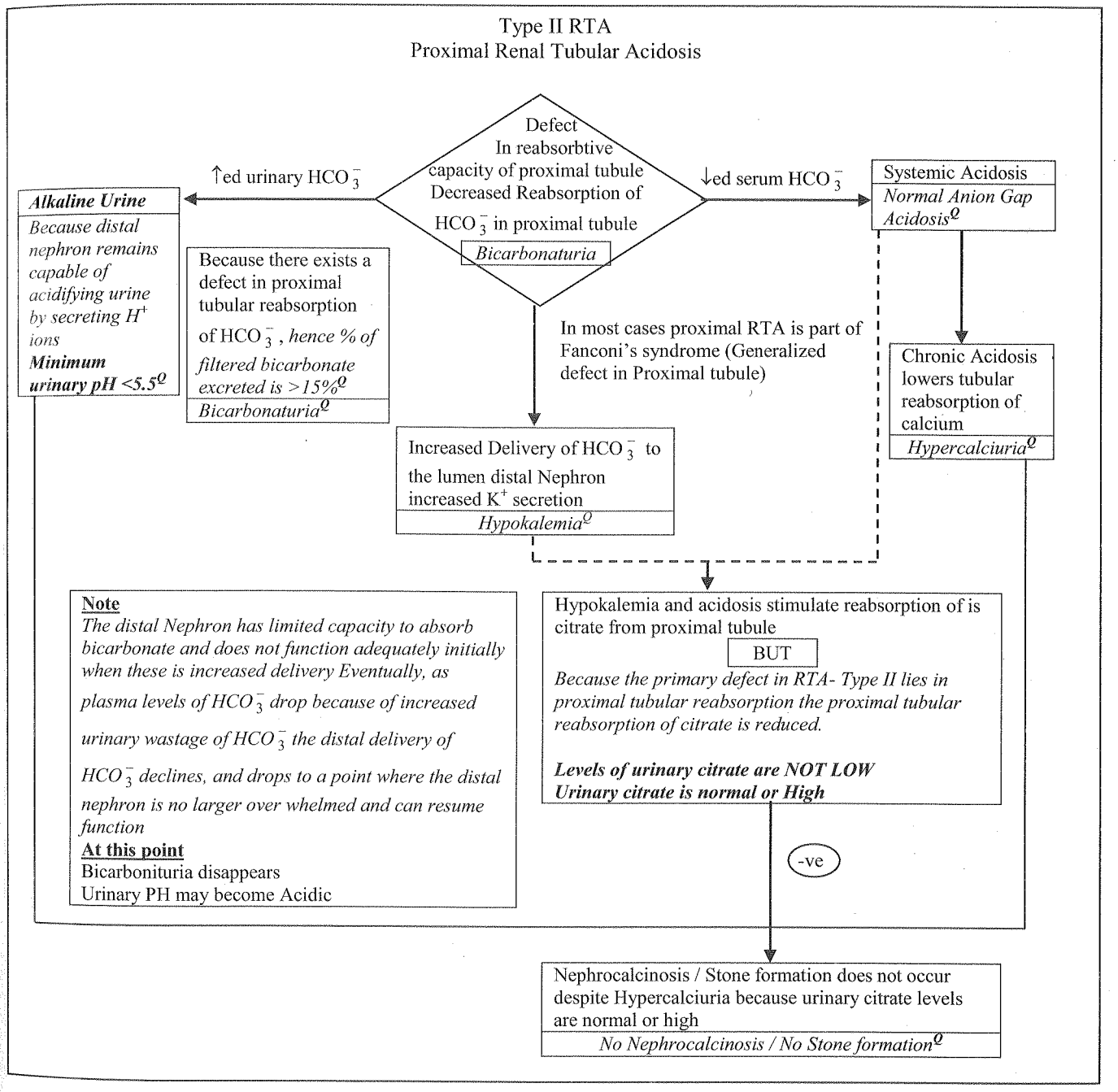
- *Secondary MPGN*
- *Cryoglobulinemic Glomerulopathy*
- *Membranous nephropathy*

***MPGN is the most common lesion.*** *These patients typically have haematuria, hypertension, proteinuria and anemia. Hypocomplementemia is very common with C4 typically more reduced than C3.*

## Renal Lesions in Leprosy

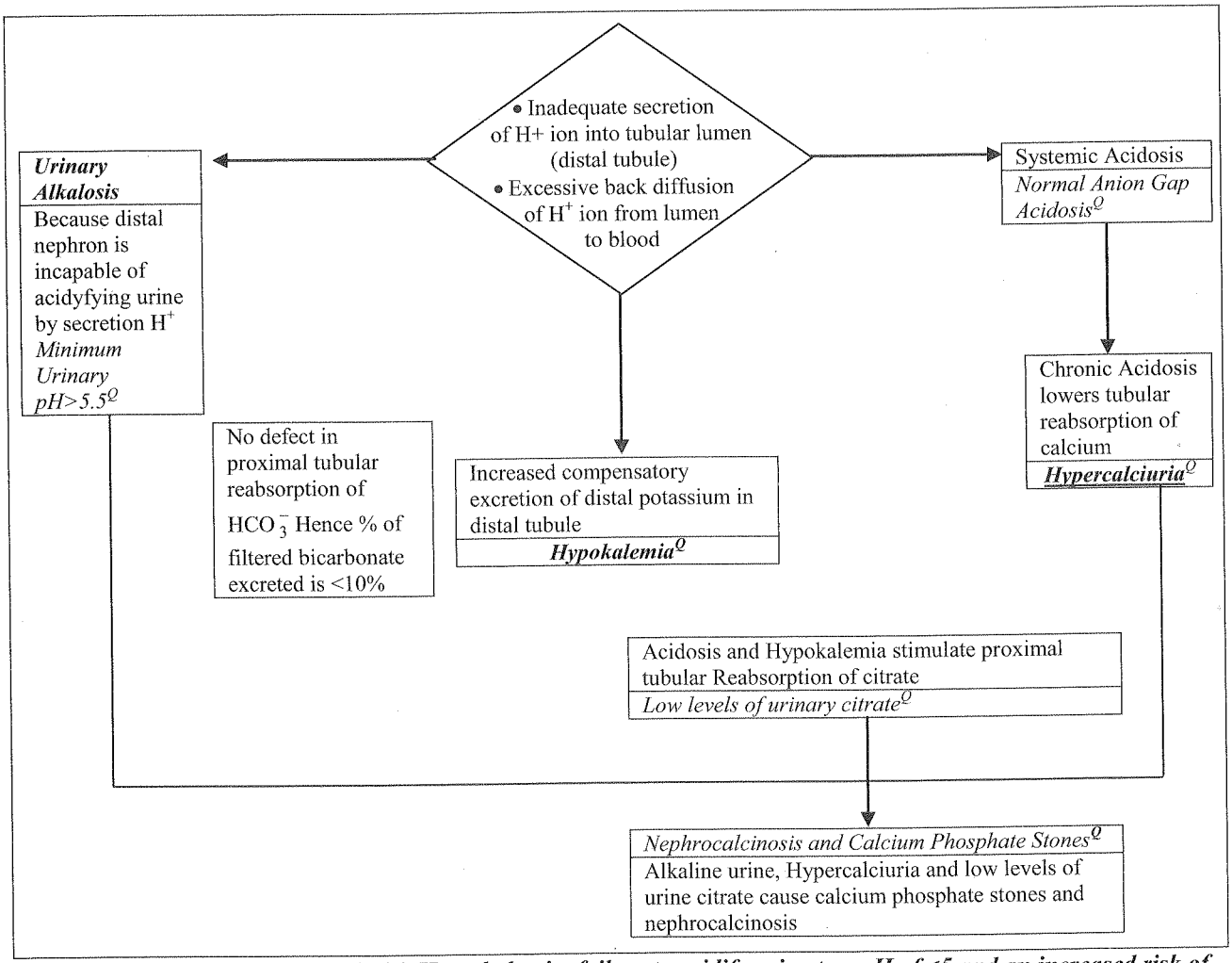
***'Chronic renal failure in leprosy is commonly due to proliferative glomerulonephritis, interstitial nephritis and renal amyloidosis and is a common cause of death'*** *– Rooks*
*Remember however that most other infectious causes lead to membranous glomerulonephritis rather than MPGN.*

## Proximal Renal Tubular Acidosis (Type II RTA)



## Distal Renal Tubular Acidosis (Type I RTA)

Type I RTA
Distal Renal Tubular Acidosis




***Type I (Distal) RTA is associated with Hyperkalemia, failure to acidify urine to a pH of <5 and an increased risk of urinary stones***

### Distinguishing Features of Various Types of Renal Tubular Acidosis

| Feature | Type I | Type II | Type IV |
|---|---|---|---|
| *Normal anion gap* | *Yes* | *Yes* | *Yes* |
| ***Minimum urine pH*** | ***> 5.5*** | *< 5.5* | *< 5.5* |
| *% Filtered bicarbonate excreted* | *< 10* | *> 15* | *< 10* |
| ***Serum potassium*** | ***Low*** | ***Low*** | ***High*** |
| *Fanconi syndrome* | *No* | *Yes* | *No* |
| ***Stones / Nephrocalcinosis*** | ***Yes*** | *No* | ***No*** |
| *Daily acid excretion* | *Low* | *Normal* | *Low* |
| *Urinary anion gap* | *Positive* | *Positive* | *Positive* |

*Type I RTA is associated with failure to acidify urine to a pH <5 because distal nephron is incapable of acidyfying urine by secretion of $H^+$(Minimum Urinary pH>5.5Q)*

## Urinary Anion Gap

### Urinary Anion Gap

Urinary Anion Gap (UAG) is defined by the difference between major urinary cations and major urinary anion

UAG = (Urine Na+ + Urine K+ ) – Urine Cl-

*Normally / Typically the UAG is nearly zero or slightly positive*

### Response to Metabolic Acidosis

In response to a metabolic acidosis, a normally functioning renal system is able to secrete additional acid in the form of ammonium $NH_4^+$, generally as NH4Cl.

While $NH_4^+$ is an unmeasured urinary cation, its presence in urine can be estimated by using the measurement of urine $Cl^-$ as a proxy since ammonium (a cation) is generally secreted with chloride (an anion) to maintain electroneutrality

#### With a Normally Functioning Renal System

***Negative UAG***

If the renal system is able to appropriately increase the secretion of ammonium in response to a metabolic acidosis, the amount of $NH_4Cl$ in the urine increases and the UAG or net charge will be negative:

(urine $Na^+$ + urine $K^+$) – (a larger amount of urine Cl-)= a negative number.

***A negative UAG*** *suggests that renal tubular dysfunction is not the cause of the metabolic acidosis.*

***This may be seen in Gastrointestinal causes of metabolic acidosis such as diarrhea***

#### If the Renal System is not functioning normally

***Positive UAG***

If, the renal system is not able to appropriately increase the secretion of ammonium in response to the metabolic acidosis, the amount of NH4Cl in the urine remains unchanged or even decreases, and the UAG or net charge will be positive:

(urine $Na^+$ + urine $K^+$)- (a smaller amount of urine $Cl^-$) = a positive number

***A positive UAG*** *suggests that there is impaired renal acid secretion and that the renal system is the cause of, or at least contributing to, the metabolic acidosis.*

***This may seen in Distal Renal Tubular Acidosis or chronic kidney disease***

## Bartter's syndrome

| *Features* | *Bartter Syndrome (Mimics Loop Diuretics)* | *Gitelman's Syndrome (Mimics Thiazide Diuretics)* |
|---|---|---|
| *Inheritance* | • ***Autosomal recessive disorder.*** | • ***Autosomal recessive disorder*** |
| *Pathophysiology* | • ***Genetic defect in the thick ascending limb of the Loop of Henle***<br>• *Defects in Na-K-2Cl co-transporter, K or Cl channels result in lack of concentrating ability* | • ***Genetic defect in the distal tubule***<br>• *Defect in Na-Cl cotransporter in the distal tubule* |
| *Age of Presentation* | • *Early in life.* | • *Late childhood or early adulthood.* |
| *Clinical presentation:* | • *No Hypertension*<br>• *Polyuria and polydipsia common*<br>• *Neuromuscular symptoms are uncommon or mild*<br>*Often presents with sensorineural deafness, triangular facies with drooping mouth, large eyes and pinnae, and renal failure.* | • *No Hypertension (Can see lower than average blood pressure due to salt wasting).*<br>• *Polyuria and nocturia in 50-80%.*<br>• *Often present with neuromuscular symptoms such as muscle cramping and spasms, significant fatigue.* |
| *Lab data:* | • *Chloride resistant metabolic alkalosis*<br>• *Hypokalemia*<br>• ***Normal serum magnesium (may be low).***<br>• ***Increased Urinary Calcium Excretion***<br>*(Hypercalciuric so at risk for kidney stones or nephrocalcinosis)* | • *Chloride-resistant metabolic alkalosis*<br>• *Hypokalemia.*<br>• ***Hypomagnesemia***<br>• ***Decreased Urinary calcium excretion***<br>• *Hypocalciuric so no increased risk of kidney stones or nephrocalcinosis)* |
| *Renal PGE2 production* | • *Increased* | • *Normal* |

*Note that serum calcium tends to be normal in patients with Gitelman's Syndrome due to lower PTH levels, Increased plasma renin and aldosterone/ K+ ratio.*

| *Presentation* | *Diagnosis* |
|---|---|
| *Hypokalemic Metabolic alkalosis* ***with Hypertension*** | *Liddle's Syndrome* |
| *Hypokalemic Metabolic Alkalosis* ***without Hypertension*** | *Bartter Syndrome (Increased Urinary Ca Excretion)*<br>*Gitelman's Syndrome (Decreased Urinary Ca Excretion)* |

# Hemolytic Uremic Syndrome

It is a vessel wall disorder charactarized by deposition of localized platelet and thrombi within the renal vasculature

**Diarrheal disease**
(E. coli 0157: H7 [Q] all over the world)
(Shigella Dysentreae type I [Q] in India & Bangladesh)
↓
Fibrin thrombus
↓
Deposition of platelet fibrin thrombus in renal vasculature

| Microangiopathic destruction of RBC | Microangiopathic destruction of platlets | Microangiopathy of renal vasculature |
|---|---|---|
| ↓ | ↓ | ↓ |
| Microangiopathic [Q] hemolytic anemia | Thrombocytopenia [Q] (Bleeding) | Renal failure [Q] (Hyperkalemia) Hypertension |

## Essentials of Diagnosis for Hemolytic Uremic Syndrome (HUS):

**HUS should be strongly suspected in any child, who presents with:**

- *Anemia,* [Q]
- *Bleeding* [Q] *(which is due to thrombocytopenia),* [Q] *or*
- *Renal failure* [Q] *(as indicated here by decreased urine output)* [Q]

Especially so, if it occurs after a diarrheal illness [Q] (due to infection with E. coli, Shigella or Salmonella)[Q].

**Essentials of diagnosis as mentioned in CMDT :**

- Microangiopathic hemolytic anemia
- Thrombocytopenia
- Renal failure
- Elevated serum LDH
- Normal coagulation tests
- *Absence of Neurological abnormality*

*There are no neurological manifestations other than those due to uraemia – CMDT*
*Neurological symptoms other than those associated with uremia are uncommon – Harrison*
*Nevertheless, confusion does prevail as Nelson confuses the issue – Extra renal manifestations may include CNS manifestations – Nelson*

## Laboratory Findings in Hemolytic Uremic Syndrome (HUS):

**Laboratory findings in HUS** – *CMDT 2002 / 556*

1. Anemia: Microangiopathic hemolytic
   Red blood cell fragmentation on peripheral smear
   Helmet cells / Burr cells
2. Thrombocytopenia
3. WBC counts rise (Nelson 16th/ 1587)
4. LDH levels are elevated out of proportion to degree of hemolysis
5. *Coomb's test is negative*
6. Tests of coagulation are normal (exclude DIC) with the exception of – elevated fibrin degradation products (explains hypofibrinogenemia)

**Treatment of Hemolytic Uremic Syndrome:**

- **Hemolytic Uremic Syndrome is often a self-limiting condition**
  '***Typical HUS (D+ HUS) is often a self limiting condition***, *although many children need extensive supportive care including dialysis, for a period of time' – 'Chronic Complex Diseases of Childhood' (Universal Publishers) 2011/363*
- ***The treatment of typical HUS (D+ HUS) is essentially supportive.***
- *No specific treatment is available.*
- *Plasmapharesis (Plasma therapy) is of little or no value (as opposed to TTP)*
- *Extensive supportive care including dialysis forms the mainstay of management*
- ***Most commonly children recover from the acute episode in 2-3 weeks (CPDT)***
- *Children with HUS may develop chronic residual renal disease or hypertension later in life and hence follow up of patients with HUS should include serial monitoring of renal function and blood pressure.*

**Differentiation of Thrombotic Thrombocytopenic Purpura and Hemolytic Uremic Syndrome**

| PENTAD of Thrombotic Microangiopathy | TTP (Pentad) | HUS (Triad) |
|---|---|---|
| *Microangiopathic Hemolytic Anemia* | +++ | +++ |
| *Thrombocytopenia* | +++ | +++ |
| *Renal Dysfunction* | +++ | +++ *(Predominates)* |
| ***Fever*** | +++ | ***+/- (Uncommon)*** |
| *Neurological Dysfunction* | +++ | *+/- (Uncommon)* |

**Fever in Hemolytic Uremic Syndrome is usually mild or absent**

*'Fever is typically mild or absent' – Hoffman's Hematology (2009)/2106*

*'HUS often presents without fever or neurological dysfunction'*
*– Washington Manual of Hematology and Oncology Subspecialty Consult (2003)/53*

**Hemolytic Uremic syndrome usually follows Haemorrhagic Colitis**

*Typical Hemolytic Uremic syndrome is diarrheal associated disease* triggered by intestinal infection with Shiga toxin or Shiga like toxin producing bacteria (This is termed as D (+) HUS).

***These cases of HUS are typically preceded by episodes of bloody diarrhea or Haemorrhagic colitis***
(Most common presenting features)

| **Typical** HUS; D (+) HUS | Atypical HUS; D (-) HUS |
|---|---|
| • *Shiga producing toxin is implicated in pathogenesis*<br>• *Usually preceded or associated with bloody diarrhea (Hemorrhagic colitis)* | • *Shiga producing toxin is not implicated in pathogenesis*<br>• *Neither preceded nor associated with bloody diarrhea* |

**Serotoxin/Shiga Like Toxin/ShigellaVerotoxin (VT) is the most common toxin implicated in the pathogenesis of HUS**

Typical Hemolytic Uremic Syndrome is a diarrhea-associated condition triggered by intestinal infection with *serotoxin/shiga like toxin producing bacteria*

- *ShigellaDysentreas type I, producing Shiga Toxin is the most common organism in India & Bangladesh*
- *Shiga like toxin (serotoxin) producing E. coli (EHEC 0157:H7) is the most common implicated agent worldwide.*

## Nephrosclerosis

| *Benign Nephrosclerosis* | *Malignant Nephrosclerosis* |
|---|---|
| *This term is used to describe the changes in kidney associated with benign phase of hypertension* | *This term is used to describe the changes in kidney associated with malignant or accelerated hypertension.* |
| *Gross* | *Gross* |
| • Kidney *size is either* normal[Q] *or may be moderately* reduced[Q] | • Kidney size *is* variable[Q] *May be* smaller in size[Q] *(when superimposed on benign nephrosclerosis) or Larger in* size *(enlarged)[Q] than normal (patients who develop malignant hypertension in pure form)* |
| • Grain leather appearance[Q] *: The cortical surface has a fine even granularity* | • Flea bitten appearance[Q]: ***The cortical surface** may show multiple small **peticheal haemorrhages**[Q] from rupture of arterioles or glomerular capillaries.* |
| *Microscopic (Vascular Changes & Parenchymal Changes)* | *Microscopic (Vascular Changes & Parenchymal Changes)* |
| • **Hyaline Arteriosclerosis** [Q] *Narrowing of the lumens of arterioles and small arteries caused by thickenning and hyalnization of the walls* | • **Fibrinoid necrosis of arterioles**[Q] **(Necrotizing arteriolitis**[Q]**)** *The vessel wall shows fibrinoid necrosis. Represents an acute event and necrosis is usually not accompanied by intense inflammation* |
| • Fibroelastic Hyperplasia[Q]*: in the intima (intimal thickenning[Q]), duplication of elastic lamina and hypertrophy of the 'media'* | • **Hyperplastic intimal sclerosis**[Q] / Onion – Skinning[Q] **Concentric laminae** *of proliferated smooth muscle cells, collagen and basement membrane* **(producing intimal thickenning)** |
| • *Parenchymal changes (due to ischaemic) Variable degree of Atrophy of parenchyma due to ischaemia* | • *Parenchymal changes (due to ischaemia) Variable degree of atrophy of paranchyma due to ischaemia. Infarction necrosis distal to abnormal vessels may be seen* |

## Causes of Contracted Kidneys

| Causes of Contracted Kidneys |
|---|
| • *Chronic Glomerulonephritis (Bilateral)* |
| • *Nephrosclerosis because of systemic hypertension (Bilateral)* |
| • *Chronic pyelonephritis (Usually unilateral)* |
| • *Global renal infarction (Unilateral)* |
| • *Radiation nephritis (Unilateral)* |
| • *Renal artery stenosis (Unilateral)* |
| • *Post obstructive atrophy (Unilateral)* |

*Note that Acute Glomerulonephritis, and acute pyelonephritis are associated with enlarged kidneys but chronic cases are associated with contracted kidneys*

# Renal Artery Stenosis

## Renal Artery Stenosis: Review

- Renal Artery stenosis is an important cause of Renovascular Hypertension
- ***Bilateral involvement is seen in half of the affected cases (50%)***

## Etiology

- Atherosclerotic disease : This is the most common cause in middle aged /elderly patients
- Fibromuscular Dysplasia : ***This is the most important cause in young females***

## Presentation

- Hypertension
  - Abrupt onset of hypertension
  - Acceleration of previously well controlled hypertension
  - Refractory Hypertension
- Features of increased sympathetic neural activity (which is associated with Renovascular disease)
  - Flushing
  - Loss of nocturnal BP decrease
  - Putonomic instability
  - Rapid BP swings
- Progressive Renal failure / Azotemia

## Diagnosis

| Magnetic Resonance Angiography (MRA) | Contrast Enhanced Arteriography |
|---|---|
| MRA is the most sensitive (>90%) and specific (95%) non invasive test for the diagnosis of RAS | Contrast enhanced angiography is the most definitive (but invasive) diagnostic procedure for diagnosis of RAS |

## Management

**Medical Therapy with ACE Inhibitors or Angiotensin Receptor Blockers**

### Indications

**Unilateral Renal artery Stenosis**

- With hypertension & normal renal function (more effective than other antihypertensives)
- With hypertension & abnormal renal function (beneficial effect on survival without affecting renal function)
- With hypertension, diabetes, proteinuria and normal or abnormal renal function (effective antihypertensives)

### Contra indications

**Bilateral Renal Artery stenosis**

ACE inhibitors or Angiotensin receptor blockers are contraindicated in patients with Bilateral renal artery stenosis or stenosis in a solitary kidney as their use in such patients leads to worsening of renal failure
(These patients are especially sensitive to decline in intraglomerular pressure)

**Note**

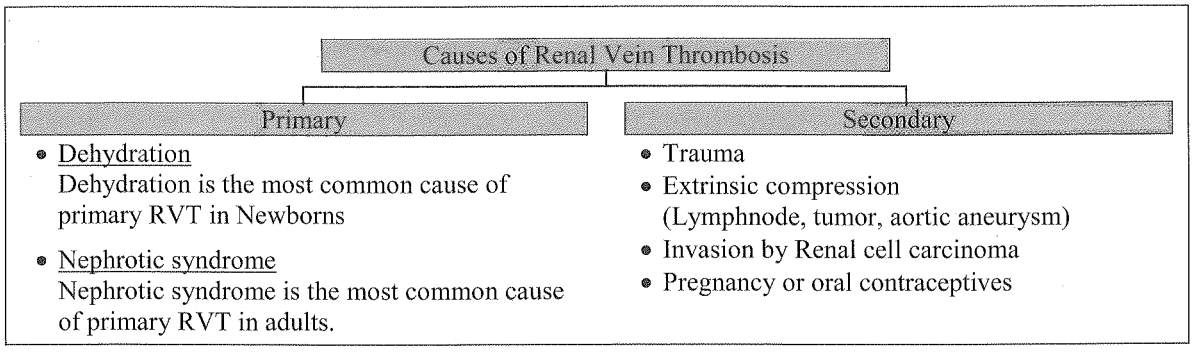
***Acute Renal Failure / Worsening of Renal Failure with Angiotension Receptor Inhibitors is a diagnostic clue to the diagnosis of renal artery stenosis (indicates bilateral disease)***

## Surgical Therapy with Angioplasty + Stent placement

*Should be considered only after optimal medical therapy has failed to achieve goal BP or resulted in a > 30% increase in serum creatinine*

# Renal Vein Thrombosis

## Causes of Renal Vein Thrombosis:




## Common Renal pathologies causing Renal Vein Thrombosis:

| **Nephrotic Syndrome: Common Renal pathologies causing Renal Vein Thrombosis** |
|---|
| • *Membranous Glomerulonephritis (strongest association)* |
| • *Membranoproliferative Glomerulonephritis* |
| • *Amyloidosis* |
| • *Lupus Nephritis (Thrombosis & hemorrhage 3rd/724)* |

*Nephrotic syndrome due to diabetic mellitus, minimal change disease and focal segmental sclerosis are rarely associated with renal vein thrombosis*

# Nephrolithiasis and Nephrocalcinosis

## Renal Calculi: Composition and Features

| Stone Type | X Ray finding | Predisposing features | Comments |
|---|---|---|---|
| **Oxalate stones** (calcium oxalates) | ***Radiopaque*** | *Hypercalciuria*<br>*Hyperoxaluria* | *Most common types of Renal Calculi* |
| **Phosphate Stones**<br>- *Calcium phosphate*<br>- *Magnesium Ammonium Phosphate (Struvite)* | *Radiopaque* | • ***Excess Alkali consumption***<br>• ***Alkaline urine***<br>• *Infection with urease splitting organisms eg. Proteus* | *Struvite stones are often solitary*<br>*Struvite stones form staghorn calculi* |
| **Cystine Stones** | *Radiopaque* | *Inherited cystinuria* | • ***Form in acidic urine***$^{Q}$<br>• *Extremely hard stones*$^{Q}$<br>• *Relatively resistant*$^{Q}$ *to fragmentation with ESWL* |
| **Uric acid stones** | *Radioluscent* | *Gout*<br>*Hyperuricemia* | • *Form in acidic urine*<br>• ***Most responsive to lithotripsy*** |
| **Xanthine stones** | *Radioluscent* | *Deficiency of xanthine oxidase* | - |

## Lithotripsy and Renal Calculi Composition

**Lithotripsy and Renal Calculi Composition**

| Composition most responsive to Lithotripsy | Composition Relatively resistant to Lithotripsy (Moderate Responsive) | Composition most Resistant to Lithotrispsy |
|---|---|---|
| *Uric acid calculi*<br>*Calcium oxalate Dihydrate* | *Struvite (Phosphate)*<br>*(Calcium oxalate Monohydrate)* | ***Cystine Calculi***<br>*(Calcium oxalate Monohydrate)* |

*Cystine stones are most resiatnt to Lithotripsy.*
*Uric acid stones are infact most responsive to Lithotripsy along with calcium oxalate dehydrate stones*

## Radio-opacity and Renal Calculi Composition

**Renal Stones**

| Radiopaque | | Radioluscent |
|---|---|---|
| • *Oxalate Stones*<br>  - *Calcium Oxalate*<br>• *Phosphate Stones*<br>  - *Calcium phosphate*<br>  - *Magnesium ammonium phosphate (struvite)*<br>• *Cystine stones* | | • *Uric Acid Calculi*<br>• *Xanthine Calculi*<br>• *Indinavir Calculi*<br>*(complication of Indinavir use-Proteinase inhibitor)*<br>• *Triametrene calculi*<br>*(complication of Triamterene use-Antihypertensive)* |

## Triple-Phosphate Stones

Triple Phosphate Stones (Phosphate stones)

- *Triple phosphate stones are composed predominantly of magnesium ammonium phosphate (strurite) with variable amounts of calcium phosphate.*
- *They form in the presence of high urinary concentration of ammonia (bicarbonate and carbonate)*
- *They form in cases of UTI when urine is infected with urea splitting bacteria i.e. Proteus, Kleibsella and Pseudomonas*
- *They form in urine with an alkaline pH.*

*Urea splitting organisms split urea to ammonia there by providing an alkaline pH which facilitates precipitation of phosphate crystals.*

## Location of Ureteric colic (pain)

### Location of Ureteric colic (pain)

Pain classically radiates from costovertebral angle, down towards the lower anterior abdominal quadrant

***In Men*** it may also be felt in the bladder, scrotum or testicles

***In Women*** it may also be felt in the vulva

Location of Ureteric Pain

| Stone in upper ureter | Stone in the midportion of ureter | | Stone in the lower portion of ureter | Stone in the intramural portion of ureter |
|---|---|---|---|---|
| | Right side | Left side | Proximal to orifice | At the level of orfice or orfice involved due to edema |
| Pain radiates to Testicles *(T11,T12)* [*Nerve supply of testicles is similar to that of kidney & upper ureter*] | Pain referred to McBurneys point and *simulates appendicitis (T12, L1)* | Pain referred to left lower quadrant and *simulates diverticulitis*[Q] or other disease of the descending or sigmoid colon *(T12, L1)* | pain is *referred to inner side of thigh or groin (L1, L2)* | Symptoms of vesical irritability such *as frequency and urgency may occur* |

## Indications and methods for removal of stone

**Indications for stone removal**

- *Repeated attacks of colic*
- *Stone is too large to pass*
- *Stone is enlarging*
- *Stone is not moving*
- *Stone is causing complete obstruction of the kidney*
- *Urine is infected*

| Ureteroscopic Removal | Extracorporal shock wave Lithotripsy | Percutaneous Nephrolithotripsy |
|---|---|---|
| • *Small stone*<br>• *Stone in lower part of ureter within 5-6 cm of ureteric orfice* | • *Best for proximal stones* that can be identified by the imaging system of Lithotriptor<br>• Stones in miduretor can be pushed up in the pelvis and *then* exposed to shock waves<br>• Not appropriate if complete obstruction is present<br>• *Stones < 2.0 to 2.5 cm can be removed* | • It is done for proximal ureteric cacluli<br>• Stones > 2.5 cm, those that are resistant to shock waves |

**Open Surgery** *is done very rarely nowadays when all methods have failed, Urethrolithotomy is done for long standing calculi not accessible by instruments and ESWL.*

# Congenital Diseases of the Kidney

## Polycystic Kidney Disease

**Polycystic Kidney Disease**

| Adult Polycystic Kidney Disease | Childhood Polycystic Kidney Disease |
|---|---|
| *Also termed as Autosomal Dominant Polycystic kidney disease (ADPKD)* | *Also termed as Autosomal Recessive Polycystic kidney Disease (ARPKD)* |

## Childhood Polycystic kidney Disease / Autosomal Recessive PKD

### Childhood Polycystic kidney Disease / Autosomal Recessive PKD : Review

Childhood Polycystic kidney disease is a rare developmental anomaly genetically distinct from Adult polycystic kidney Disease ***having an autosomal recessive inheritance***

#### Genetics

- *Autosomal Recessive inheritance*
- Defective gene is the PKHD1 (Polycystic kidney and Hepatic Disease 1)
- PKHD1 gene codes for a protein 'Fibrocystin' (defective protein in ARPKD)[Q]

#### Epidemiology

- Majority of patients present during infancy (first year of life)
- May present later in life (in young adults)

#### Presentation

- Presentation is variable and depends on age at presentation

| Respiratory Symptoms | Renal Features | Hepatic Features |
|---|---|---|
| Respiratory distress | • Hypertension<br>• Renal failure<br>• Enlarged kidneys (abdominal mass)<br>• Pyuria<br>• Proteinuria | • Hepatomegaly<br>• Features of portal Hypertension<br>-Esophageal varices<br>-Hypersplenism |

#### Associations

- **Maternal Oligohydramnios**
  Oligohydramnios may be present due to severe intrauterine kidney disease
- **Potter's syndrome**
  Most severely affected neonates may have Potter's syndrome due to oligohydramnios
- **Pulmonary Hypoplasia**
  *Pulmonary hypoplasia may result from severe oligohydramnios and as part of Potter's sequence*
  *'About 50% of affected neonates die of pulmonary hypoplasia' - Harrison's*
- **Congenital Hepatic fibrosis**
  *Congenital Hepatic Fibrosis is a peculiar type of hepatic fibrosis characterized by bland periportal fibrosis, and proliferation of well differentiated biliary ductules*
  **Hepatic cysts may be seen** (In almost all cases liver has cysts with portal fibrosis - Robbins)
- **Biliary Ductal Atresia**
  ARPKP is invariably associated with congenital hepatic fibrosis and various degrees of biliary ductal Atresia

#### Renal Pathology

- Kidney's are enlarged (invariably Bilateral)
- Numerous small cysts are present in kidney which give it ' Sponge like appearance'
- Cysts are primarily located in distal tubule and collecting duct
- ***Cysts may be discovered prenatally, at birth or later in life***

## Adult Polycystic kidney: Autosomal Dominant PKD

**Inheritance : Autosomal Dominant**

**Pathology:**

- Kidneys are grossly enlarged with multiple cysts
- Cyst are distributed uniformly throughout cortex and medulla
- Cysts contain straw coloured fluid that may become haemorrhagic

**Presentation:** usually occurs in III$^{rd}$ / IV$^{th}$ decade

| Renal | Extra renal manifestation |
|---|---|
| 1. Pain: due to infection (Pyelonephritis) / obstruction / sudden haemorrhage | 1. Cysts: Liver (most common) Spleen, pancreas and ovaries |
| 2. Haematuria $^{Q}$ | 2. Intracranial aneurysms |
| 3. Nocturia: due to impaired concentrating ability | 3. Colonic diverticular disease |
| 4. Nephrolithiasis (15-20%) $^{Q}$ | 4. Cardiac: Mitral valve prolapse / AR / TR |
| 5. Hypertension (75% adults and 25% children) : due to activation of rennin angiotensin system. $^{Q}$ | |
| 6. Progressive decline in renal function – CRF | |

## Cystic Disease of Renal Medulla

Cystic Disease of Renal Medulla

### Nephrophtysis – Medullary cystic kidney

Both these conditions may progress to end stage Renal disease and present with similar clinical features.

#### Nephrophthysis

- Autosomal Recessive
- Age of onset in 1$^{st}$ decade (Juvenile)
- Progression to ESRD occurs <20 years of age
- Growth Retardation is present as it affects growing children
- Extra renal abnormalities are frequent and include
  *Retinitis pigmentosa*
  *Cerebellar Ataxia*
  *Hepatic fibrosis*
  *Skeletal abnormalities*

#### Medullary Cystic kidney

Autosomal dominant

Age of onset in 3$^{rd}$ or 4$^{th}$ decade (Adult)

- Progression to ESRD occurs >20 years to age
- Growth retardation is usually not associated as it affects adults
- Extra renal abnormalities are absent.

### Medullary Sponge kidney

This is a relatively benign condition

## Juvenile Nephronophthisis

### Juvenile Nephronophthisis

Chronic Tubulo-interstitial Nephritis which uniformly progresses to End stage Renal Disease.

**Extrarenal Abnormalities**[Q]

*Ritinitis Pigmentosa*
*Cerebellar Ataxia*
*Hepatic Fibrosis*
*Skeletal Anomalies*

*Autosomal Recessive disease*[Q]

Pathology Triad

- Tubular Basement Membrane Disintegration
- Tubular cyst formation (Medullary Cyst)
- Tubulo interstitial inflammation

*Kidney size is normal or Reduced (shrunken)*[Q]

#### Loss of Urinary Concentrating Ability

*Polyurea*[Q] — *Nocturnal*
*Polydipsia*[Q] — *Enuresis*[Q]

*Low urinary osmolarity which does not increase after desmopressin administration*

#### Salt wasting

- *Hyponatremia*[Q]
- *Hypovolumia (dehydration)* [Q]
- *Hypotension (low BP)* [Q]

#### Progressive Renal failure

Because of loss of urinary concentrating ability and salt wasting, typical symptoms of renal failure do not occur until late in disease

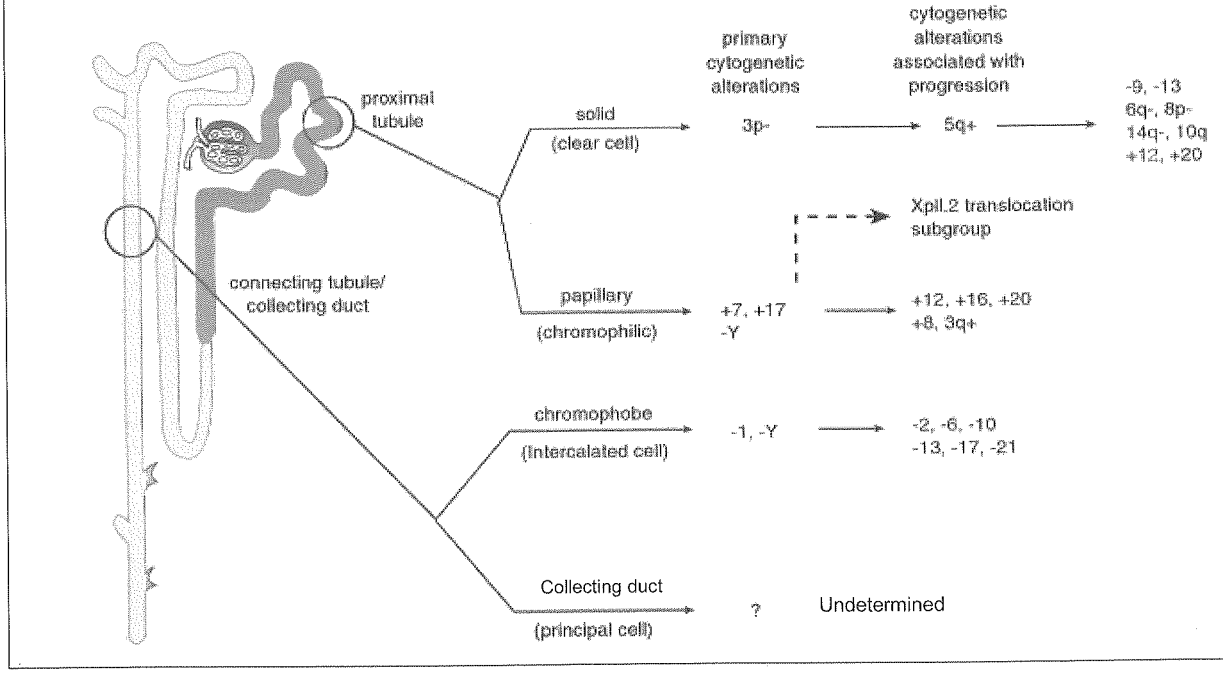
*Edema, Hypertension, Hematuria and proteinuria do not occur until late in disease*

- *Anemia*[Q]
- *Growth Retardation*[Q]
- *Elevated BUN/creatinine*[Q]

## Renal Neoplasms

**Classification of epithelial neoplasms arising from the kidney**

| Carcinoma Type | Cell of Origin | Cytogenetics |
|---|---|---|
| Clear cell | Proximal tubule | 3p deletions (3p-), VHL gene mutations, 5q gains |
| Papillary | Proximal tubule | Trisomy of chromosome 7 and 17 (+7, +17)<br>Loss of Y chromosome (-Y) |
| ***Chromophobe*** | ***Cortical collecting duct*** | ***Hypodiploid / Monosomy***<br>***Loss of multiple chromosomes 1, 2, 6, 10, 13, 17, 21 & Y*** |
| Oncocytic | Cortical collecting duct | Undetermined<br>Either karyotypically normal or contain limited number of karyotypic abnormalities including -1, -Y and translocations involving chromosme II |
| Collecting duct | Medullary collecting duct | Undetermined<br>Losses of multiple chromosomes 1, 6, 14, 15 & 22 |



## Features of three major histological variants of renal call carcinoma:

**Features of three major histological variants of renal call carcinoma:**

| Clear cell carcinoma (Non papillary) | Papillary carcinoma | Chromophobe renal carcinoma |
|---|---|---|
| • Most common ♀ type ♀ (70-80%)<br>• Cells have clear ♀ or granular cytoplasm and are non papillary<br>• Defect lies in chromosomes 3 ♀ | • Second most common type (10-15%)<br>• Papillary ♀ growth pattern is characteristic (clear cell not seen)<br>• Psammoma bodies may be present<br>• Most common cytogenetic abnormality are<br>- trisomy of chromosome 7, 16 & 17 and loss of Y in male patients in sporadic form<br>- trisomy 7 in familial form<br>• ♀ Striking characteristic of tumor is: **Tendency to invade the renal vein** and grow as a solid column of cells within the vessels. Extension may produce a continuous cord of tumor in IVC and even in the right side of heart. | • Least common (5%)<br>• Pale eosinophilic cytoplasm<br>• Multiple chromosomal losses and extreme haploploidy |

## Classic Triad of Renal cell carcinoma

Classic Triad of Renal cell carcinoma (seen in 10-20% of patients)

- *Hematuria (Gross)*
- *Pain (Abdominal / Flank)*
- *Mass (Abdominal / Flank)*

## Paraneoplastic Syndromes is Renal Cell Carcinoma

**Paraneoplastic Syndromes is Renal Cell Carcinoma**

| Characteristic Paraneoplastic Syndromes (common) | Other Paraneoplastic Syndromes (Less common / Not characteristic) |
|---|---|
| • ***Erythrocytes/Polycythemia*** (due to ↑ed erythropoietin)<br>• ***Hypercalcemia*** (due to ↑ed parathyroid related peptide)<br>• ***Hypertension*** (due to ↑ed rennin production )<br>• *Non metastatic Hepatic Dysfunction (Stauffer syndrome)* (due to ↑ed granulocyte-macrophage colony stimulating factor) | • Cushing's syndrome (due to ↑ ACTH production)<br>• Galactorrhea (due to ↑ed prolactin production)<br>• Hypoglycemia (due to ↑ed Insulin)<br>• Gynaecomastia & decreased libido (due to ↑ gonadotropins)<br>• Hirsuitism, amenorrhea and male pattern balding (due to ↑ gonadotropins)<br>• Amyloidosis<br>• Leukemoid Reaction and Eosinophilia<br>• Dysfibrinogenemia |

*Note that while Harison's textbook does not include Cushing's syndrome in the list of paraneoplastic syndromes associated with Renal cell carcinoma, this condition is clearly mentioned as an associated paraneoplastic syndrome in other standard textbooks like Robbin's and Smith's Urology.*

# Wilm's Tumor

## Typical Congenital Malformations seen in association with Wilm's Tumor:

**Wilm's Tumor**

The risk of Wilm's tumor is increased in associations with at least three recognizable groups of congenital malformations associated with distinct chromosomal loci

| WAGR syndrome | Denys Drash Syndrome | Beckwith Wiedemann Syndrome |
|---|---|---|
| Characterized by:<br>• *Wilm's tumor*<br>• ***Aniridia***<br>• *Genital Anomalies*<br>• *Retardation (Mental)* | Characterized by:<br>• *Gonadal Dysgenesis* ***(male pseudohermaphroditism)***<br>• *Early onset nephropathy (diffuse mesangial sclerosis/renal failure)* | Characterized by:<br>• *Organomegaly*<br>• *Macroglossia*<br>• ***Hemihypertrophy***<br>• *Omphalocele*<br>• *Adrenal cytomegaly (Abnormal large cells in Adrenal cortex)* |

## Staging Systems used for the staging of Wilm's Tumor

Two Staging Systems are currently being used for the staging of Wilm's Tumor

**Pre-chemotherapy Staging System**

- *Developed by the National Wilm's Tumor staging Group (NWTSG) (NWTSG – Staging system)*
- This staging system is widely used in North America and Canada
- *'NWTSG' approach involves employment of 'primary Surgery'. Chemotherapy with or without Radiation therapy is given after surgery*
- ***Staging is done at time of surgery (Pre – chemotherapy)***
- Primary advantage is more accurate staging

Primary Surgery (Nephrectomy)

↓

**Staging (at surgery)**
**(Pre-chemotherapy staging)**

↓

Postoperative Chemotherapy / Radiation

**Post-chemotherapy Staging System**

- *Developed by the International Society of Pediatric Oncology (SIOP) (SIOP – Staging system)*
- This staging system is widely used in Europe
- 'SIOP' Approach involves employment of preoperative chemotherapy without histological confirmation of Wilm's tumor. (Primary chemotherapy for all patients regardless of extent)
- ***Staging is done at time of surgery (Post-chemotherapy)***
- Primary advantage is easier surgical removal of tumor with decreased tumor rupture due to shrinkage of tumor by preoperative chemotherapy

Primary Chemotherapy (Preoperative)

↓

Surgery (Nephrectomy)

↓

**Staging (at surgery)**
**(Post-chemotherapy staging)**

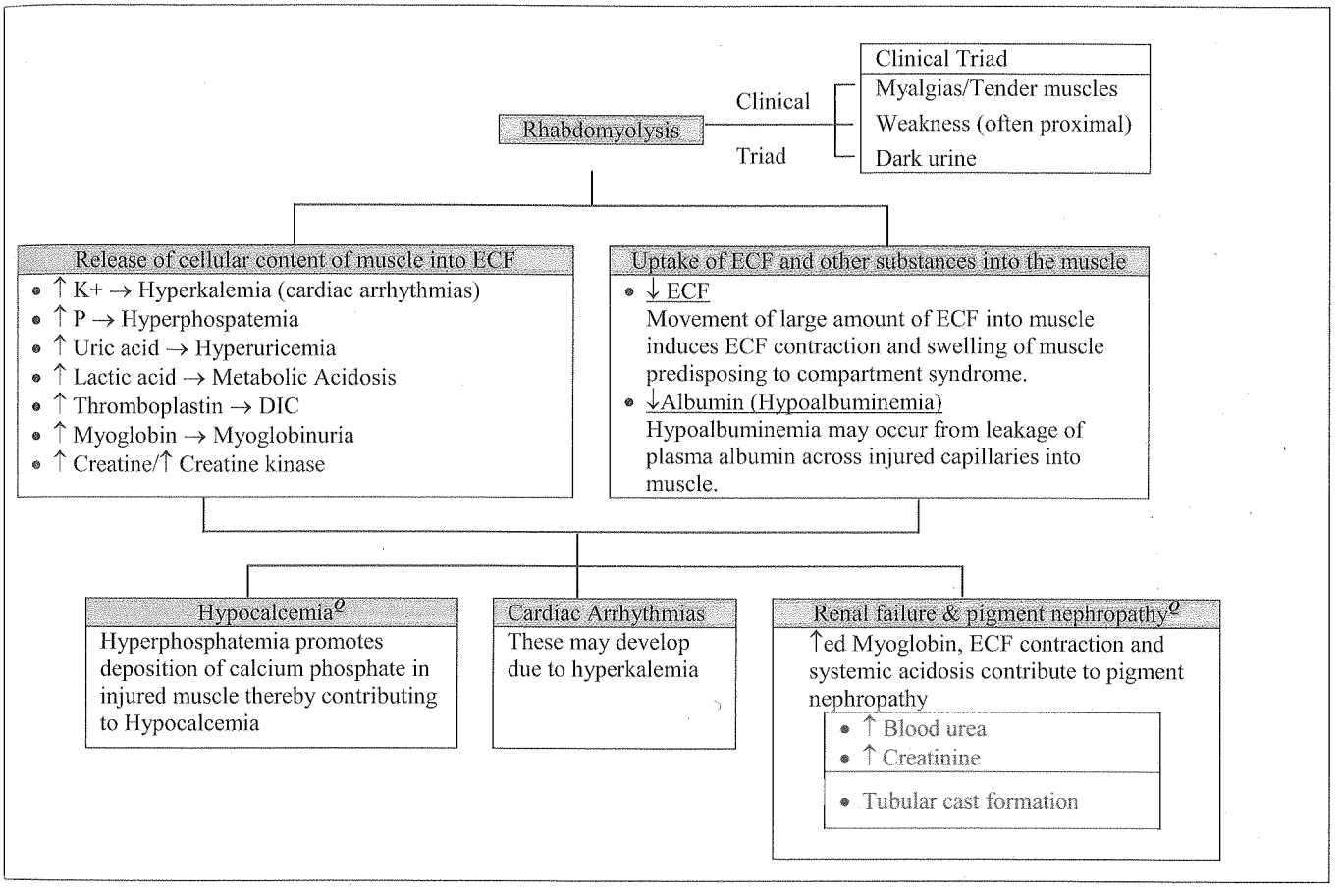
↓

Postoperative chemotherapy / Radiation

Both Staging Approaches (NWTSG and SIOP) have improved survival for patients with Wilm's tumor Success rates of treatment with both approaches are comparable

# Rhabdomyolysis /Crush Syndrome

## Rhabdomyolysis




## Classical Triad of Crush Syndrome

**Crush Syndrome (Rhabdomyolysis)**
**(SystemicManifestation of severe crush injury)**

| Hypotension | Renal Failure (ARF) | Metabolic Complication |
|---|---|---|
| • Shock<br>• Compartment<br>• Syndrome | • Myoglobinuria<br>*Rhabdomyolysis results in the release of myoglobin, potassium phosphorus & creatinine into the circulation* | • Hyperkalemia<br>• ***Hypocalcemia***<br>• ***Hyperphosphatemia***<br>• Metabolic Acidosis<br>Cardiac arrhythmias may result secondary to metabolic comp. |

**Note –**

*Crush syndrome is associated with Hypocalcemia and not hypercalcemia. Systemic hypocalcemia results from inflow of calcium into muscle calls through leaky sarcolemmal membranes*[Q].

# Ureteropelvic Junction Obstruction (UPJ Obstruction)

## Ureteropelvic Junction Obstruction (UPJ Obstruction)

- UPJ obstruction is the *most common obstructive lesion in childhood*[Q] and is the *most common cause of hydronephrosis found on prenatal and early postnatal ultrasonography*[Q].
- It is most commonly caused by intrinsic stenosis of a segment of ureter which is usually localized to the region of pelviureteric junction. Other causes include ureteric folds & extrinsic obstruction by crossing lower pole vessels.

## Presentation

- ***Hydronephrosis*** revealed by maternal USG ***(Dilated renal pelvis but normal ureter)***
- Palpable Renal Mass in new borns or infants
- ***Abdominal flank or Back pain typically*** exacerbated by drinking large volumes of liquid
- UTI / Haematuria after minimal trauma

## Epidemiology

- Left side more commonly involved than right (Bilateral = 10%)
- Male more commonly involved than females (M:F= 2:1)

## Initial Diagnosis by Ultrasonography

- ***Hydronephrosis with dilated renal pelvis***
- Ureter if visualized is of normal caliber (not delated)

## Renal Differential function

Nuclear Renography is used to determine Renal Differential function

- ***A differential function of <40% is considered significant and often an indication for surgical management***
- *Differential function of < 10% is often considered an arbitrary cut off for nephrectomy*

Management of PUJ

### Conservative

Differential Renal function > 40% is usually managed conservatively especially when AP diameter of PUJ < 30 mm

### Surgical

- Differential Renal Function < 40% is usually an indication of surgical management especially if AP diameter of PUJ > 30 mm
- Deteriorating Renal function (a decrease in differential function by more than 10% on follow up USS).
- Persistant symptoms of pain, UTI
- Concern that the function of kidney will decline if it is left untreated (AP diameter of renal pelvis may indicate this).

#### Procedure of choice

**Pyeloplasty *is the surgical procedure of choice***

- ***Open pyeloplasty is considered the traditional gold standard***
- Laporascopic pyeloplasty is gaining growing acceptance

#### Other procedures

- External Drainage (Nephrostomy)
- Endopyelotomy
- Nephrectomy

**External Drainage (Nephrostomy)**

This is used to provide temporary drainage particularly when children present with pyonephrosis or ***when differential renal function is <10-15%*** to assess potential recovery of function before considering definitive surgery.

**Endopyelotomy**

Endopyelotomy involves incising the UPJ junction by either a retrograde or antegrade route, by a minimally invasive approach. ***The success rate is inferior to open pyeloplasty. A large hydronephrosis and differential renal function <20% are considered relative contraindications for Endopyelotomy.***

**Nephrectomy**

Nephrectomy may be considered when renal differential function is very low and the likelihood of functionl recovery is minimal. ***Most pediatric urologists consider an arbitrary cut off for differential function in the range of 10-15%.*** However a reconstructive procedure (pyeloplasty) should always be considered as the procedure of choice to salvage the kidney.

# Hepatorenal Syndrome

## Hepatorenal syndrome

- Hepatorenal syndrome is defined as a state of functional renal failure (Reduced GFR) in patients with severe liver disease
- ***Structurally /Histologically the kidneys are normal and recover function after successful liver transplantation.***
- The pathogenetic hallmark of hepatorenal syndrome is intense renal vasoconstriction with coexistent systemic vasodilatation
- The diagnosis of hepatorenal syndrome is considered in accordance with the following diagnostic criteria.

## Diagnostic of Hepatorenal Syndrome

### Major criteria

- *Low glomerular filtration rate, as indicated by serum creatinine > 1.5 mg/dL or 24-hr creatinine clearance < 40 mL/min*
- *Absence of shock, ongoing bacterial infection, fluid losses, and current treatment with nephrotoxic drugs*
- *No sustained improvement in renal function (decrease in serum creatinine to 1.5 mg/dL or increase in creatinine clearance to 40 mL/min) after diuretic withdrawal and expansion of plasma volume with 1.5L of a plasma expander*
- *Proteinuria <500 mg/dL and no ultrasonographic evidence of obstructive uropathy or parenchymal renal disease*

### Additional criteria

- *Urine volume < 500 mL/d*
- *Urine sodium < 10 meq/L*
- *Urine osmolality greater than plasma osmolality*
- *Urine red blood cells <50/high- power field*
- *Serum sodium concentration < 130 mEqL*

Note: All major criteria must be present for the diagnosis of hepatorenal syndrome. Additional criteria are not necessary for the diagnosis but provide supportive evidence.

# QUESTIONS

## Urinalysis

1. Urinalysis shows RBC casts; likely source is :
   A. Kidney *(AI 2001)*
   B. Ureter
   C. Bladder
   D. Urethra
2. Presence of which of the following in the urine is diagnostic of glomerular injury: *(AIIMS- June 99)*
   A. Bright red cells
   B. 20% dysmorphic RBC's
   C. 100 RBC per high power field
   D. beta 2 micro globulin
3. Feature of glomerular haematuria (select two options): *PGI June 05)*
   A. Dysmorphic R.B.C
   B. Fragmented R.B.C.
   C. Full of R.B.C.
   D. Gross haematuria
   E. R.B.C. cast
4. Presence of which of the following in the urine is diagnostic of glomerular injury: *(AIIMS June 99)*
   A. Bright red cells
   B. 20% dysmorphic RBC's
   C. 100 RBC per high power field
   D. Beta 2 micro globulin
5. In hematuria of glomerular origin the urine is characterized by the presence of all of the following *except*: *(AI 2004)*
   A. Red cell casts
   B. Acanthocytes
   C. Crenated red cells
   D. Dysmorphic red cells
6. Recurrent gross hematuria is seen in (select two best options): *(PGI Dec 2000)*
   A. Alports's syndrome
   B. IgA nephropathy
   C: Focal segmental glomerulosclerosis
   D. Membranous nephropathy
7. Presence of which of the following correlates best with renal pathology *(AIIMS June 2000)*
   A. Hyaline cast
   B. Coarse granular cast
   C. Broad cast
   D. Epithelial cast
8. Which of the following is indicative of renal tubular disease *(AIIMS May 01)*
   A. Hyaline casts
   B. Coarse granular casts
   C. Cystine Oxalate cells
   D. White cell casts
9. A boy is suffering from acute pyelonephritis. Most specific urinary finding will be- *(AIIMS May 07)*
   A. W.B.C. casts
   B. Leucocyte esterase test
   C. Nitrite test
   D. Bacteria in gram stain
10. Acute pyelonephritis and uncomplicated UTI may be differentiated by all of the following Except :
    A. WBC cast *(AI 2008)*
    B. Concentrating defect
    C. Organisms in excess of 100,000 cfu/ml
    D. Antibody to Tomm Horsfall protein
11. In differentiating Glomerular proteinuria from Tubular proteinuria, Glomerular proteinuria is indicated by: *(PGI June 05)*
    A. Proteinuria >3.0 – 3.5 g/day
    B. Globulin > Albumin
    C. Albumin to β2 microglobulin ratio of 100:1
    D. Tomm Harsfall protein
12. Which of the following statements about orthrostatic proteinuria is true: *(PGI Dec 2000)*
    A. Seen in recumbent position
    B. Is benign
    C. Future risk of nephrotic syndrome
    D. < 300 mg/day
13. Bence Jones proteins are derived from: *(AI 2010)*
    A. Alpha Globulins
    B. Beta Globulins
    C. Gamma Globulins
    D. Delta Globulins
14. Bence Jones proteinuria may be seen in: *(AI 2010)*
    A. Alpha heavy chain disease
    B. Gamma heavy chain disease
    C. 'Mu' heavy chain disease
    D. Epsilon heavy chain disease
15. In a child, non-functioning kidney is best diagnosed by: *AI 2005)*
    A. Ultrasonography.
    B. IVU.
    C. DTPA renogram.
    D. Creatinine clearance.
16. A patient presented with ARF with complete anuria, but a normal ultrasound. Next investigation is: *(AI 99)*
    A. IVP
    B. Antegrade pyelography
    C. Retrograde pyelography
    D. Radio renogram
17. A patient presents with acute renal failure with normal ultrasound abdomen report. Next most useful investigation is : *(AIIMS June 99)*
    A. Intravenous pyelography

B. DTPA scan
C. Retrograde pyelography
D. X-ray abdomen and CT scan.

18. In urinary system disease, GI symptoms appears because of : *(AIIMS June 98)*
A. Chemical reaction
B. Renogastric reflex
C. Peritoneal reaction
D. Reflux phenomenon

19. Which of the following best methods of urine collection is associated with least contamination :
A. Suprapubic aspiration *(AI 2008)*
B. Mid stream collection
C. Catheterization
D. Urine Bag specimen

20. Most common agent causing catheter induced urinary tract infection is: *(NBE)*
A. E.Coli
B. Pseudomonas
C. Staphylococcus epidermidis
D. Proteus

21. Coloured urine is not seen in : *(AI 2008)*
A. Quinine
B. Rifampcin
C. Nitrofurantoin
D. Pyridium

22. Anuria in clinical practice is defined as:
A. Urine output < 100 ml/hr *(NBE)*
B. Urine output < 400 ml/hr
C. Urine output < 800 ml/hr
D. Urine output < 1200 ml/hr

23. Which of the following best defines Microscopic Hematuria as: *(NBE)*
A. 3 or More RBC/HPF
B. 5 or More RBC/HPF
C. 25 or More RBC/HPF
D. 50 or More RBC/HPF

24. Chyluria is associated with passage of urine which is: *(NBE)*
A. White
B. Dark yellow
C. Straw coloured
D. Brown

25. The most common cause of Chyluria is: *(NBE)*
A. Carcinoma
B. Tuberculosis
C. Filariasis
D. Trauma

26. Creatinine Clearance test is used to assess: *(NBE)*
A. Glomerular Filtration
B. Proximal Tubulr Function
C. Distal Tubular Function
D. Renal Plasma Flow

27. Which of the following is the most accurate method to assess decline in GFR during initial stages of Renal insufficiency *(NBE)*
A. Serum creatinine
B. Creatinine Clearance
C. Serum BUN
D. Serum Urea

28. Which of the following statements about creatinine clearance test is true: *(NBE)*
A. Creatinine clearance test is the most accurate / gold standard test for assessing GFR
B. Creatinine clearance may overestimate the actual GFR as renal function declines
C. Creatinine clearance may underestimate the actual GFR as renal function declines
D. Creatinine clearance is more accurate than Inulin clearance in estimating GFR

29. Water Deprivation Test is used to assess *(NBE)*
A. Glomerular Function
B. Proximal Tubular Function
C. Distal Tubular Function
D. Renal Plasma Flow

## Renal Failure & Tubulointerstitial Diseases

### Acute Renal Failure:

30. Most unlikely cause of acute tubular necrosis amongst the following is : *(AI 1999)*
A. Severe-bacterial-infection
B. Massive burn
C. Severe crush injury in the foot
D. Rupture of aortic aneurysm

31. The Diuretic Phase of Acute Renal Failure is typically begins after: *(NBE)*
A. 1st Day
B. 3nd Day
C. 14th Day
D. 28th Day

32. Uremic complications typically arise during which of the following phases of Renal Failure: *(NBE)*
A. Initiation
B. Maintenance
C. Diuretic Phase
D. Recovery Phase

33. Continuous Renal Replacement Therapy is initiated in which of the following phases of Acute Renal Failure: *(NBE)*
A. Initiation
B. Maintenance
C. Diuretic Phase
D. Recovery Phase

34. Causes of Acute Tubular necrosis include:
A. Radiocontrast agents *(PGI June 07)*
B. Psrsproteins
C. Amphoterecin B
D. Abruptio placentae
E. All of the above

35. Which of the following values are suggestive of acute tubular necrosis : *(AIIMS Nov. 2000)*
    A. Urine osmolality>500
    B. Urine sodium>40
    C. Blood urea nitrogen/plasma creatinine>20
    D. Urine creatinine /plasma creatinine>40
36. Fractional excretion of sodium <1 is seen in
    A. Prerenal azotemia *(AIIMS Nov- 07)*
    B. Acute tubular necrosis
    C. Acute ureteral obstruction
    D. Interstitial nephritis
37. Pre-renal azotemia is associated with one of the following characteristic feature : *(AIIMS Nov. 2000)*
    A. Urinary $Na^+$ < 10 mmol/L
    B. Renal failure index > 1
    C. Osmolality < 500
    D. Urinary creatinine / P. creatinine ratio < 20
38. Pre-Renal Azotemia is characterized by all of the following. Except : *(AI 2010)*
    A. Fractional Excretion of Na < 1%
    B. Urinary osmolality > 500 mosm/kg
    C. Urinary sodium concentration > 40 meq/l
    D. Reversible with replacement fluids
39. Plasma urea / creatinine ratio of 20:1 may be seen in :
    A. Rhabdomyolysis *(AI 2010)*
    B. Ureteric calculi
    C. Pre-renal failure
    D. Chronic Glomerulonephritis
40. Prerenal and renal azotemia is differentiated on the basis of: *(PGI Dec 99)*
    A. Creatinine clearance
    B. Serum creatinine level
    C. Sodium fraction excretion
    D. Urine bicarbonate level
41. In tubular necrosis, ratio of urine to plasma creatinine is: *(PGI Dec 99)*
    A. 20
    B. 40
    C. 20-30
    D. 30-40
42. Which of the following is true about Acute Tubular Necrosis *(PGI June 07)*
    A. Urine specific gravity > 1.020
    B. Urine osmolality >350 mosmol/kg
    C. Urine Na < 10meq/L
    D. Blood urea : creatinine ratio < 20
43. All of the following are true about Prerenal Azotemia, Except: *(PGI June 05)*
    A. Urinary Cr/Plasma Cr >40
    B. $FE_{Na}$ < 1
    C. Urinary output < 400ml/day
    D. Plasma BUN/Creatinine ratio <20
    E. Urinary sodium concentration < 20meq/l
44. Which differentiating prerenal azotemia with ATN features favouring pre-renal azotemia (select two options): *(PGI Dec 2002)*
    A. Urine osmolality > 500 mosmol/kg
    B. Sodium <10 mmol/l
    C. Plasma transferrin/Ig ratio
    D. Fractional excretion of sodium >1
    E. Plasma BUN/creatinine ratio < 20
45. All of the following are true about Oliguric ARF
    A. Anemia *(AI-1993)*
    B. Metabolic Acidosis
    C. Uremia
    D. Hypercalcemia
46. Oliguric phase of renal failure, all are TRUE, EXCEPT: *(AIIMS May 93)*
    A. Hypercalcemia
    B. Hyponatremia
    C. Anaemia
    D. Hyperkalemia
47. Non Oliguric Acute Renal Failure is typically associated with *(NBE)*
    A. Aminoglycoside toxicity
    B. Contrast Induced Nephrotoxity
    C. Hemolytic Uremic syndrome
    D. Glomerulonephritis
48. All of the following are seen in oliguric phase of Acute Tubular necrosis, Except: *(AI 1992)*
    A. Hypernatremia
    B. Hypermagnesemia
    C. Hyper uricemia
    D. Hyper phosphatemia
49. Hypophosphatemia is seen in all except :
    A. Acute renal failure *(AI 2007)*
    B. Resolving phases of diabetic ketocidosis
    C. Respiratory alkalosis / COPD
    D. Chronic alcoholism

## Chronic Renal Failure

50. Feature of CRF include all, except: *(PGI June 05)*
    A. Impotence
    B. Restless legs
    C. Isothenuria
    D. Broad cast in urine
    E. All of the above
51. Decrease in GFR is apparent in which of the following stages of Chronic Kidney Disease
    A. Stage I *(NBE)*
    B. Stage II
    C. Stage III
    D. Stage IV
52. Azotemia appears when residual GFR is: *(NBE)*
    A. 50% -80 % of normal
    B. 20-50% of normal
    C. 10 -20% of normal
    D. < 5% of normal

53. Signs and symptoms of a Renal Failure first appear when Renal function deteriorates by more than:
A. 20% *(NBE)*
B. 40%
C. 60%
D. 80%

54. Overt symptoms of Renal failure become evident when Renal Function Deteriorates by more than
A. 40-50% *(NBE)*
B. 50-60%
C. 70-80%
D. >90%

55. Chronic Renal Failure is defined as Residual renal functional mass less than: *(NBE)*
A. 50%
B. 80%
C. 20%
D. 5%

56. Most common cause of CRF in adults is: *(NBE)*
A. Tuberculosis
B. Hypertension
C. Diabetes Mellitus
D. Glomerulonephritis

57. Restless leg syndrome (RLS) is seen in: *(AI 2009)*
A. Hypercalcemia
B. Hyperphosphatemia
C. Chronic renal failure
D. Hyperkalemia

58. Central nervous system manifestation in chronic renal failure are result of all of the following, *except*:
A. Hyperosmolarity *(AI 2003)*
B. Hypocalcemia
C. Acidosis
D. Hyponatremia

59. Chronic Renal Diseases / failure is commonly associated with *(NBE)*
A. Metabolic Acidosis
B. Metabolic Acidosis
C. Respiratory Acidosis
D. Respiratory Acidosis

60. Which of the following electrolyte abnormalities is not seen in CRF: *(NBE)*
A. Hypercalcemia
B. Hyperkalemia
C. Hyperphosphatemia
D. Hyperuricemia

61. Metabolic complication in CRF include all of the following *except* : *(AI 1998)*
A. Hyperkalemia
B. Hypophosphatemia
C. Hypocalcemia
D. Hypokalemia

62. Which of the following metabolic complications is not seen in Chronic Renal Failure: *(NBE)*
A. Hyperkalemia
B. Hyponatremia
C. Hypercalcemia
D. Hyperphosphatemia

63. Renal osteodystropy differs from nutritional and genetic forms of osesteomalacia in having :
A. Hypocalcaemia *(AI 2002)*
B. Hypercalcemia
C. Hypophostaemia
D. Hyperphosphatemia

64. Which of the following types of glomerulonephritis is least likely to cause CRF: *(AI 1999)*
A. Post streptococcal glomerulonephritis
B. Membranous GN
C. Membrano proliferative GN
D. Focal segmental glomerulosclerosis

65. Nail and half nail sign, seen in uremia is
A. Due to melanin deposition *(AIIMS May- 07)*
B. Increased capillary density at the distal half of nails
C. Hypoproteinemia
D. Circulating toxin

66. All of the following are indications of emergent dialysis, Except: *(NBE)*
A. Uremic encephalopathy
B. Persistent Hyperkalemia
C. Refractory volume overload
D. Azotemia

67. All improves after dialysis except: *(AIIMS Nov 08)*
A. Pericarditis
B. Peripheral neuropathy
C. Metabolic acidosis
D. Seizure

68. CRF with anemia best treatment: *(NBE)*
A. Oral Iron Therapy
B. Erythropoietin Stimulating Agents
C. Blood transfusion
D. Androgenic Steroids

69. The initial treatment of choice for secondary hyperparathyroidism in renal osteodystrophy is:
A. Cinacalcet *(NBE)*
B. Bisphosphonates
C. Calcium restriction
D. Phosphate binders

70. Most common cause of death in chronic dialysis patient is: *(NBE)*
A. Cardiovascular Disease
B. Infection
C. Malignancy
D. Anemia

71. Most common cause of death in patients on dialysis for Acute Renal Failure is: *(NBE)*
A. Cardiovascular Disease
B. Infection
C. Malignancy
D. Anemia

72. Trace elements in Dialysis patients associated with risk of Osteomalacia: *(NBE)*
   A. Lead
   B. Iron
   C. Aluminium
   D. Zinc

73. Dialysis disequilibrium occurs due to:
   A. Reverse Urea effect *(NBE)*
   B. Hypertension
   C. Alumunium toxicity
   D. Amyloid deposition

74. A girl aged 8 years has been admitted for dialysis. She has serum K of 7.5 meq/l, which is the fastest way to reduce the hyperkalemia? *(AI 2009)*
   A. Kayexalate enema
   B. Infusion of insulin + glucose
   C. IV calcium gluconate
   D. IV $NaHCO_3$

75. A patient in Chronic renal failure presents with tall peaked T waves on ECG. Management includes: (select two options) *(PGI June 05)*
   A. IV K-bicarbonate
   B. KCl
   C. $CaCl_2$
   D. Sodium bicarbonate

76. All of the following are used for treatment of hyperkalaemia except : *(AIIMS May' 06)*
   A. Calcium gluconate
   B. Sodium bicarbonate
   C. Intravenous infusion of glucose with insulin
   D. Beta blockers

77. Most common viral infection after Kidney Transplantation is: *(NBE)*
   A. EBV
   B. HSV
   C. CMV
   D. HBV

78. A Child with kidney transplant developed lymphoproliferative cancer. The most common virus implicated is: *(NBE)*
   A. CMV
   B. Varicella
   C. HPV
   D. EBV

## Tubulointestinal Disease

79. All of the following antibiotics are known to cause acute interstitial nephritis, except : *(NBE)*
   A. Erythromycin
   B. Sulphonamides
   C. Ciprofloxacin
   D. Aminoglycosides

80. Interstitial nephritis is seen with all except:
   A. Beta lactam inhibitors *(AIIMS May 07)*
   B. INH
   C. Diuretics
   D. Allopurinol

81. Salt losing nephritis is a feature of : *(AI 2000)*
   A. Interstitial nephritis *(AIIMS 95)*
   B. Renal Amyloidosis *(AIIMS May 94)*
   C. Lupus nephritis
   D. Post Streptococcal Glomerulonephritis

82. Necrotizing papilities is seen in all of the following except: *(AIIMS May 02)*
   A. Salicylate poisoning
   B. Renal vascular thrombosis
   C. PNH
   D. Diabetes mellitus

83. Necrotizing pappillitis may be seen in all of the following conditions *except* : *(AI 2002)*
   A. Sickle cell disease
   B. Tuberculous pyelonephritis
   C. Diabetes mellitus
   D. Analgesic nephropathy

84. Necrotizing pappillitis is seen in : *(AIIMS 2002)*
   A. Salicylate poisoning
   B. Glomerulonephritis
   C. PNH
   D. Diabetes insipidus

85. Necrotizing pappillitis is seen in all of the following *except* : *(AIIMS May 02)*
   A. Salicylate poisoning
   B. Renal vascular thrombosis
   C. PNH
   D. Diabetes mellitus

86. Renal papillary necrosis is almost always associated with one of the following conditions :
   A. Diabetes-mellitus *(AI 99)*
   B. Analgesic-nephropathy
   C. Chronic pyelonephritis
   D. Post streptococcal GN

87. Which of the following is associated with Renal Papillary Necrosis *(NBE)*
   A. Alcohol
   B. Heroine
   C. Morphine
   D. Tramadol

## Glomerular Diseases

### Nephrotic Syndrome

88. All are true of Nephrotic syndrome, *except* :
   A. RBC casts in urine *(AI 2000)*
   B. Hypo-proteinemia
   C. Oedema
   D. Hyperlipidemia

89. All of the following are decreased in Nephrotic syndrome *except* : *(AI 1997)*
A. Transferrin
B. Ceruloplasmin
C. Albumin
D. Fibrinogen

90. All of the following proteins are decreased in Nephrotic syndrome. Except *(PGI 2012)*
A. Transferrin
B. Fibrinogen
C. Albumin
D. Thyroxine Binding Globulin

91. All of the following are decreased in nephrotic syndrome *except* : *(AIIMS 1998)*
A. Serum transferrin
B. Serum fibrinogen
C. Serum ceruloplasmin
D. Serum albumin

92. Hypercoagulation in Nephrotic syndrome is caused by: *(AI 2010)*
A. Loss of Antithrombin III
B. Decreased Fibrinogen
C. Decreased Metabolism of Vitamin K
D. Increase in protein C

93. Which is seen in nephrotic syndrome (select two options): *(PGI June 99)*
A. Low serum calcium
B. Raised AT – III
C. Low lipid
D. Platelet activation

94. Nephrotic syndrome may be associated with:
A. ↓ Total cholesterol *(PGI 2000)*
B. ↓ LDL cholesterol
C. ↓ VLDL cholesterol
D. ↓ Triglycerides
E. ↓ HDL cholesterol

95. Most common cause of nephrotic range proteinuria in an adult is: *(AI 2007)*
A. Diabetes Mellitus
B. Amyloidosis
C. Hypertensive nephropathy
D. Wegner's Granulomatosis

96. The Finnish type of congenital nephrotic syndrome occurs due to gene mutations the following protein:
A. Podocin *(AI 2009, 08)*
B. Alpha – actinin
C. Nephrin
D. CD2 activated protein

97. A patient with nephrotic syndrome on longstanding corticosteroid therapy may develop all the following *except*: *(AI 2002)*
A. Hyperglycemia
B. Hypertrophy of muscle
C. Neuropsychiatric symptoms
D. Suppression of the pituitary adrenal axis

## Nephritic Syndrome and RPGN

98. Following are features of Acute GN except:
A. Polyuria *(PGI June 97)*
B. Hematuria
C. Red cell cast
D. Oliguria

99. Post-infective glomerulonephritis present as:
A. ARF *(AI 1996)*
B. Nephrotic syndrome
C. Nephritic syndrome
D. Asymptomatic hematuria

100. Cresentirc Glomerulonephritis may be seen in all of the following Except? *(AI 2008)*
A. Post Streptococcal Glomerulonephritis (PSGN)
B. Henoch Schonlein Purpura (HSP)
C. Anti Basement Membrane Disease
D. Alport syndrome

101. Crescent formation is characteristic of the following glomerular disease: *(AI-2002)*
A. Minimal change disease
B. Rapidly progressive glomerulonephritis
C. Focal and segmental glomerulonephritis
D. Rapidly non progressive glomerulonephritis

102. All can cause R.P.G.N., *except* : *(AIIMS June 97)*
A. Minimal change glomerulonephritis
B. Poststreptococcal glomerulonephritis
C. Wegener granulomatosis
D. S.L.E.

103. RPGN occurs in A/E: *(AIIMS Sep 96)*
A. SLE
B. Post streptococcal glomerulonephritis
C. Diabetic nephropathy
D. Good pastures syndromes

104. Which of the following conditions are assoiciated with pauci – immune crescenteric glomerulonephritis:
A. Henoch – Schonlein Nephritis *(AI 2009)*
B. Lupus Nephritis (SLE)
C. Microscopic polyangitis
D. Nephritis in Alport's syndrome

105. All are features of RPGN *except*
A. Rapid recovery *(AIIMS June 1997)*
B. Crescent formation
C. Hypertension
D. Non-selective proteinuria

106. The prognosis of rapidly prolifeating glomerulonephritis (Crescentric GN) depends upon –
A. Number of crescents *(AIIMS Nov 01)*
B. Size of crescents
C. Shape of crescents
D. Cellularity of crescents

107. Non –proliferative Glomerulonephritis include all of the following, Except: *(AI 2008)*
A. Focal Segmental Glomerulonephritis (FSGS)
B. Mesangiocapillary Glomerulonephritis
C. Membranous Glomerulonephritis
D. Amyloidosis

108. A 30-year-old man presents with generalized edema and hypertension. Urine examination shows subnephrotic proteinuria (< 2gm) and microscopic hematuria. Serum complement levels are decreased and he is positive for anti-hepatitis C antibodies. The most likely diagnosis is: *(AI 2012)*
   A. Post streptococcal Glomerulonephritis (PSGN)
   B. Cryoglobulinemia
   C. Membranoproliferative Glomerulonephritis (MPGN)
   D. Focal Segmental Glomerular Sclerosis (FSGS)

109. A 60-year-old woman presents with generalized edema, skin ulceration and hypertension. Urine examination shows subnephrotic proteinuria (<2gm) and microscopic haematuria. Serum complement levels are decreased and she is positive for anti-hepatitis C antibodies. The likely diagnosis is: *(AI 2012)*
   A. Post-streptococcal Glomerulonephritis
   B. Essential Mixed Cryoglobulinemia
   C. Membranoproliferative Glomerulonephritis (MPGN)
   D. Focal SegmentalGlomerulosclerosis (FSGS)

## IgA Nephropathy and PSGN

110. Which of the following is not true about Berger's disease? *(AI / AIIMS)*
   A. The pathological changes are proliferative and usually confined to mesangial cells; usually focal and segmental
   B. Hematuria may be gross or microscopic
   C. On immunofluorescence deposits contain both IgA and IgG
   D. Absence of associated proteinuria is pathognomonic

111. IgA-nephropathy is seen in: *(AIIMS June 2000)*
   A. Membranous glomerulonephritis
   B. Mesangioproliferative glomerulonephritis
   C. Focal glomerulonephritis
   D. Cresentic glomerulonephritis

112. Increased IgA deposits are seen in:
   A. Henoch Schonlein Purpura *(AIIMS June 2000)*
   B. Minimal Change Glomemlonephritis
   C. Chronic Pyelonephritis
   D. Haemolytic Uremic Syndrome

113. A 6 yr child presents with recurrent episodes of gross hematuria for 2 yrs. He is likely to have: *(AI 2008)*
   A. IgA nephropathy
   B. Wilm's tumour
   C. Henoch Schonlein Purpura (HSP)
   D. Neuroblastoma

114. The most common presentation of IgA nephropathy is: *(NBE)*
   A. Nephritic syndrome
   B. Nephritic syndrome
   C. Microscopic hematuria
   D. Repeated gross hematuria

115. A feature of Renal vaculitis in children is -
   A. IgA raised *(AIIMS- Sep- 96)*
   B. Antinuclear antibody in serum
   C. Low complement level
   D. Cytoplasmic antinuclear Ab in serum

116. Marker for the renal vasculitis in children is –
   A. Increased IgA level *(AI 98)*
   B. Low complement level
   C. ↑ Antineutrophilic cytoplasmic antibody titre
   D. Increase antinuclear antibody

117. 12 years old Shyam presented with gross hematuria with 80% dysmorphic RBC's 2 days after a attack of upper respiratory tract infection. Diagnosis is –
   A. Microangiopathic thrombotic anaemia
   B. IgA Nephropathy *(AIIMS Nov- 01)*
   C. PSGN
   D. H.S. purpura

118. A six year old male baby presents to a hospital with recurrent gross hematuria for 2 years. There is no h/o burning micturition or pyuria. Urine routine examination demonstrated no pus cells and urine culture was sterile. Serum C3 levels were normal. What is the most probable diagnosis –
   A. Wilm's tumour *(AIPGMEE-08)*
   B. IgA nephropathy
   C. Post –streptococcal glomerulonephritis
   D. Urinary tract infection

119. A young man develops gross heamaturia 3 days after an attack of URTI; likely renal pathology is:*(AI 2001)*
   A. Acute glomerulonephritis
   B. Minimal change disease
   C. IgA nephropathy
   D. Membranous glomerulonephritis.

120. A female patient Nandini presents with upper respiratory tract infection. After 15 days, she develops hematuria. Probable diagnosis is:
   A. IgA nephropathy *(AIIMS June 99)*
   B. Wegener's granulomatosis
   C. Henoch scholein purpura
   D. Post streptococcal glomerulonephritis.

121. True about Post-Streptococcal Glomerulonephritis is:
   A. 50% of cases occur after pharyngitis
   B. Early treatment of Pharyngitis eliminates the risk of P.S.G.N. *(AI 2000)*
   C. Glomerulonephritis, secondary to skin infection, is more common in summer
   D. Recurrence is seen

## Goodpasture's Syndrome

122. A patient presents with hemoptysis and hematuria few weeks after a respiratory tract infection. ANCA antibodies are present. Likely diagnosis is:
   A. Goodpasture's syndrome *(AI 1995)*

B. IgA Nephropathy
C. Nephrotic syndrome
D. PSGN

123. Rama, a 20 year old smoker, presents with hemoptysis and hematuria. Likely diagnosis is:
A. Good pasture's syndrome *(AI 1997)*
B. Nephrotic syndrome
C. Gullian Barre syndrome
D. IgA Nephropathy

124. A 22 year old presents to his physician with hemoptysis and hematuria with basement membrane antibodies. Most likely diagnosis is: *(NBE)*
A. Wagner's Granulomatosis
B. Goodpasture's syndrome
C. PAN
D. Churg-Strauss syndrome

125. Good pasture's syndrome is charachterized by:
A. Anti-GBM antibodies *(PGI June 99)*
B. Crescenteric glomerulonephritis
C. Diffuse alveolar haemorrhage
D. All of the above

126. Good pasture's syndrome is characterized by all of the following, except: *(AIIMS May 08)*
A. Glomerulonephritis
B. Leucocytoclastic Vasculitis
C. Diffuse alveolar haemorrhage
D. Presence of antibodies to Basement Membrane

## Alport's Syndrome

127. Association of deafness & nephritis is seen in –
A. Pickwickian syndrome *(AIIMS May 93)*
B. Alport's syndrome
C. Fabry's disease
D. Lawrence Moon Biedl syndrome

128. A 25 year old boy presents with renal failure. His uncle died of renal failure three years ago. Slit lamp examination reveals Lenticonus / Keratoconus. The likely diagnosis is: *(AIIMS Nov 2010)*
A. Autosomal Dominant Polycystic Kidney (ADPCKD)
B. Autosomal Recessive polycystic kidney (ARPCKD)
C. Alport's syndrome
D. Denysh-Drash Syndrome

129. Mutation in alpha 5 chain of collagen 4. The diagnosis – *(AIIMS Nov- 06)*
A. Alport's syndrome
B. Thin membrane disease
C. Nodular glomerulosclerosis
D. Good pasture syndrome

130. Presenting manifestation of Alport syndrome is :
A. Haematuria *(AIIMS Feb 97)*
B. Proteinuria
C. Oliguria
D. Sensorineural deafness

131. Disease, does not recur in the kidney after renal transplant is : *(AIIMS Feb 97)*
A. Alport syndrome
B. Amyloidosis
C. Good Pasteur's syndrome
D. Diabetic nephropathy

## Minimal Change Nephropathy

132. A 7 year old boy presented with generalized edema. Urine examination revealed marked albuminuria. Serum biochemical examinations showed hypoalbuminaemia with hyperlipidemia. Kidney biopsy was undertaken. On light microscopic examination, the kidney appeared normal. Electron microscopic examination is most likely to reveal –
A. Fusion of foot processes of the glomerular epithelial cells *(AIIMS Nov-03)*
B. Rarefaction of glomerular basement membrane
C. Deposition of electron dense material in the basement membrane
D. Thin basement membrane

133. A 7 year old girl is brought with complaints of generalized swelling of the body. Urinary examination reveals Grade 3 proteinuria and the presence of hyaline and fatty casts. She has no history of Hematuria. Which of the following statements about her condition is true: *(AI 2009)*
A. No IgG deposits or C3 deposition on Renal biopsy
B. Her C3 levels will be low
C. IgA Nephropathy is the likely diagnosis
D. Alport's syndrome is the likely diagnosis

134. True about light microscopy in minimal change disease is: *(AIIMS 2001)*
A. Loss of foot process seen
B. Anti GBM Abs seen
C. IgA deposits seen
D. No change seen

135. True about Light microscopic changes in Minimal Change Glomerulonephritis is: *(AI 95)*
A. No abnormality
B. Fusion of foot process
C. Absence of Immunoglobulins
D. Absence of complement

136. True about Minimal change disease is : *(AI)*
A. Appears normal under light microscopy but electron microscope shows loss of foot processes.
B. Mesangial deposits
C. Tram Track appearance
D. Gross haematuria

137. A child presents with hematuria and nephrotic syndrome. A diagnosis of minimal change disease was made. Which of the following statements about the diagnosis is true: *(All India)*

A. Glomerular function is lost due to loss of polyanions around the foot processes
B. Foot processes of podocytes in the Glomerular membrane are normal
C. Glomerular function is lost due to deposition of IgA on the glomerular membrane
D. Focal segmental changes are observed

138. Typical features of Lipoid nephrosis include:
A. Normal light microscopy *(PGI 2009)*
B. FSGS
C. Glomerular tuft sclerosis
D. Effacement of foot processes
E. Tubular sclerosis

139. Clinical features of minimal change : glomerulonephritis are *all except* *(AI 1996)*
A. Hypertension
B. Edema
C. Selective proteinuria
D. Fever

140. Minimal change glomerulopathy may be seen in association with all of the following except :
A. Hepatitis B *(AIIMS Nov. 05)*
B. HIV
C. Drug - induced interstitial nephritis
D. Hodgkin's disease

141. All are steroid resistant *except:* *(AI 96)*
A. Post-streptococcal glomerulonephritis
B. Minimal change glomerulonephritis
C. RPGN
D. Recurrent hematuria

## Diabetic Glomerulopathy

142. Most common pathological features in diabetes mellitus is : *(AI 1998)*
A. Papillary necrosis
B. Diffuse glomerulosclerosing
C. Renal atherosclerosis
D. Chronic pyelonephritis

143. Which of the following is the first clinically detectable sign of diabetic nephropathy *(NBE)*
A. Serum creatinine
B. Creatinine clearance
C. Microalbuminuria
D. Macroalbuminuria

144. The earliest clinical feature of diabetic nephropathy is: *(NBE)*
A. Microalbuminuria
B. Increased serum creatinine
C. Nephritic syndrome
D. Hematuria

145. Preferred method for determining microalbuminuria is: *(NBE)*
A. Urinary dipsticks
B. 24 hour urinary protein collection
C. Urinary A/C Ratio in a spot voided sample
D. Urinary A/C Ratio in a 24 hour collection

146. Pathological changes of diabetic nephropathy are *all except:* *(AI 1995)*
A. Fibrin caps and capsular drops
B. Intercapillary glomerulosclerosis
C. Focal sclerosis
D. Capillary basement membrane thickening

147. The Recommended treatment of early diabetic nephropathy manifested by microalbuminuria is
A. Strict glycemic control
B. Low protein Diet
C. Strict glycemic control and Low Protein Diet
D. Strict glycemic control, Low protein Diet and ACE Inhibitors

## HIV Glomerulopathy

148. Most characteristic GN in HIV is: *(PGI Dec99)*
A. FSGN
B. MPGN
C. MCD
D. RPGN

149. HIV renal specific nephropathy is: *(NBE)*
A. Focal Segmental Glomerulosclerosis
B. Membranoproliferative Glomerulonephritis
C. Mesangioproliferative Glomerulonephritis
D. Membranous Glomerulonephritis

150. HIV associated nephropathy is a type of:
A. Membranous glomerulonephritis *(AIIMS Nov 04)*
B. Immunotaetoid glomerulopathy
C. Collapsing glomerulopathy
D. Fibrillary glomerulopathy

151. Collapsing glomerulopathy, features: *(NBE)*
A. Tuft necrosis
B. Mesangiolysis
C. Proliferation of parietal epithelium cells
D. Hypertrophy of visceral epithelium cells

## Lupus nephritis

152. In Lupus nephritis, characteristic kidney lesion is:
A. Mesangial proliferation *(PGI Dec 98)*
B. Tubular fibrin deposits
C. Wire loop lesions
D. IgG deposits

153. Wire loop lesions are often characteristic for the following class of lupus nephritis: *(AIIMS May 04)*
A. Mesangial proliferative glomerulonephritis(WHO class II)
B. Focal proliferative glomerulonephritis (WHO class III)
C. Diffuse proliferative glomerulonephritis (WHO class IV)
D. Membranous glomerulonephritis (WHO class V)

154. All of the following factors are associated with adverse prognosis and high risk of Renal progression in Lupus Nephritis, Except: *(PGI Dec 03)*

A. High levels of Anti-ds DNA
B. Persistant proteinuria (Nephrotic range > 3gm/day)
C. Hypocomplementenemia
D. Anti LA (SSB)

## Amyloid Nephropathy

155. A patient who has been diagnosed with bronchiectasis 5 years ago presents with edema on legs and proteinuria. The most likely finding in his kidney will be: *(AI 2012)*
A. Minimal Change Disease
B. Amyloid Nephropathy
C. Rapidly Progressive Glomerulonephritis (RPGN)
D. Crescenteric Glomerulonephritis

## Leprotic Glomerulopathy

156. In Leprosy most common renal lesion seen is:
A. MGN *(AI 1999)*
B. MPGN
C. Focal glomeruloselerosis
D. Diffuse glomerulosclerosis

## Miscellaneous Glomerulonephritis

157. Reflux Nephropathy with protenuria in the nephrotic range may be seen in patients with : *(AIIMS Nov 06)*
A. Membranous glomerulonephritis
B. Focal segmental Glomerulosclerosis
C. Nodular glomerulosclerosis
D. Crescenteric glomerulonephritis

158. A 30 year old man presents with generalized edema and hypertension. Urine examination shows subnephrotic proteinuria (< 2gm) and microscopic hematuria. Serum complement levels are decreased and he is positive for antihepatitis C antibodies. The most likely diagnosis is : *(AI 2007)*
A. Post streptococcal Glomerulonephritis (PSGN)
B. Mixed cryoglobulinemia
C. Membranoproliferative glomerulonephritis (MPGN)
D. Focal symentat Glomerular sclerosis (FSGS)

159. A 60 year old woman presents with generalized edema, skin ulceration and hypertension. Urine examination shows subnephrotic proteinuria (<2gm) and microscopic haematuria. Serum complement levels are decreased and she is positive for anti-hepatitis C antibodies. The likely diagnosis is :
A. PSGN *(AI 2007)*
B. Essential mixed cryoglobulinemia
C. Membrano proliferative glomerulonephritis
D. Focal segmental glomerulosclerosis

160. Serum C3 is persistently low in the following except:
A. Post streptococcal glomerulonephritis
B. Membranoproliferative glomerulonephritis
C. Lupus nephritis *(AI / AIIMS)*
D. Glomerulonephritis related to bacterial endocarditis

161. All of the following are associated with low complement levels *except*: *(AII India)*
A. Lupus nephritis
B. Mesangio capillary glomerulonephritis
C. Diarrhea-associated hemolytic uremic syndrome
D. Post-infections glomerulonephritis

162. Hypocomplementemia is seen (select three options):
A. PSGN *(PGI June 2008)*
B. Membranous GN
C. Focal segmental DN
D. MPGN
E. Infective endocarditis.

163. Non –proliferative Glomerulonephritis include all of the following, Except: *(AI 2008)*
A. Focal Segmental Glomerulonephritis (FSGS)
B. Mesangiocapillary Glomerulonephritis
C. Membranous Glomerulonephritis
D. Amyloidosis

164. Proliferative glomerular deposits in kidney are found in
A. Amyloidosis *(AI-2000)*
B. Diabetes mellitus
C. IgA nephropathy
D. Membranous glomerulonephritis

## Renal Tubular Acidosis

165. Type II RTA is associated with all of the following, EXCEPT *(AI-1990)*
A. Normal Anion Gap Acidosis
B. Hyper calciuria
C. Decreased urinary citrate
D. Minimum urinary pH < 5.5

166. Type IRTA is associated with all of the following, Except: *(AI 1993)*
A. Urinary PH > 5.5
B. Normal Anion Gap Acidosis
C. ↑ urinary calcium
D. ↑ urinary citrate

167. Which of the statements about Renal Tubular Acidosis type I (Type I RTA) is not true: *(AI 2012)*
A. Failure to acidify urine to a pH < 5
B. Associated with increased risk of urinary stones
C. Associated with Hyperkalemia
D. Treatment involves alkali replacement as bicarbonate

168. Distal renal tubular acidosis is associated with: *(NBE)*
A. Oxalate stones
B. Citrate
C. Calcium stones
D. Uric acid stones

169. Proximal & distal renal tubular acidosis is differentiated by all, except: *(AIIMS June 98)*

A. Stones in kidney
B. Hypokalemia
C. Daily acid secretion
D. Presence of Fanconi syndrome

170. All are features of renal tubular acidosis type I, except : *(AIIMS Sept 96)*
A. Stone in kidney
B. No anion gap
C. Hypokalemia
D. Fanconi syndrome

171. Positive Urinary Anion Gap helps to establish the diagnosis of : *(AI 2009)*
A. Alcoholic ketoacidosis
B. Diabetic ketoacidosis
C. Renal tubular Acidosis
D. Acidosis in Diarrhea

172. Dent's disease is characterised by all except: *(NBE)*
A. Chloride channel defect
B. Affects males more than females
C. Low Molecular Weight proteinuria
D. Distal Renal Tubule defect

## Disorders of Renal Vasculature

### HUS

173. An 8 yrs old boy presents to casualty with history of diarrhoea, followed by decreased urine output. Blood examination shows thrombocytes 90,000/$cm^3$. Diagnosis is : *(AI 2000)*
A. Hemolytic Uremic Syndrome.
B. Disseminated Intravascular Coagulation
C. Hemophilia
D. Idiopathic Thrombocytopenic Purpura

174. Which of the following statements about Hemolytic Uremic Syndrome is least correct: *(AI 2012)*
A. Usually follows Haemorrhagic colitis
B. Often self-limited
C. Fever is usually mild or absent
D. Serotoxin has no role in pathogenesis

175. All are features of haemolytic uremic syndrome, *except*: *(AIIMS Dec 95)*
A. Hyperkalemia
B. Anaemia
C. Renal microthrombi
D. Neuropsychiatric disturbances

176. All of the following statements are true about Hemolytic uremic syndrome *except* : *(AI 1997)*
A. Uraemia
B. Hypofibrinogenemia
C. Thrombocytopenia
D. Positive coomb's test

177. A 20 year old male presents with features of acute renal failure 5 days after an episode of diarrhea. Blood examination shows thrombocytopenia and Hb-10 gm%. Likely cause is: *(AIIMS June 99)*
A. Haemolytic uremic syndrome
B. Hereditary spherocytosis
C. Haemolytic crises
D. Chronic glomerulonephritis

### Benign /Malignant Hypertension

178. Which of the following changes does not occur in malignant hypertension : *(AI 2008)*
A. Peticheal Haemorrhages on cortical surface
B. Fibrinoid necrosis of arterioles
C. Intimal concentric thickening
D. Hyaline arteriosclerosis

179. Commonest histoloical finding in Benign Hypertension is: *(AI 2009)*
A. Proliferative endarteritis
B. Necrotizing arteriolitis
C. Hyaline arteriosclerosis
D. Cystic Medial Necrosis

180. Which characteristic feature is seen in the kidney in Malignant hypertension: *(AI 1994)*
A. Hyaline necrosis
B. Fibrinoid necrosis
C. Medial wall hyperplasia
D. Micro-aneurysm

181. Common pathological changes seen in kidney in benign hypertension are: *(AI 97)*
A. Fibronoid necrosis
B. Microaneurysm
C. Hyaline arteriosclerosis
D. Thining of walls

### Renovascular Hypertension

182. Increased renin activity is seen in all of the following, except: *(NBE)*
A. Benign nephrosclerosis
B. Malignant nephrosclerosis
C. Haemolytic Uremic Syndrome
D. Juxtaglomerular cell tumour

183. Low Renin Hypertension is seen in all of the following, Except: *(NBE)*
A. Essential hypertension
B. Conn's syndrome
C. Renovascular hypertension
D. Liddle's syndrome

184. Low Renin Hypertension is seen in all of the following, Except: *(NBE)*
A. Congenital Adrenal Hyperplasia
B. Conn's syndrome
C. Renovascular hypertension
D. Liddle's syndrome

185. Which of the following is the most specific and sensitive screening test for Renovascular Hypertension. *(AIIMS May 01)*
   A. HRCT
   B. CT Angiography
   C. Captopril enhanced radionucleatide scan
   D. MRI

186. Which of the following is the most specific screening test for renovascular hypertension: *(PGI 2008)*
   A. Magnetic Resonance Angiography (MRA)
   B. Spiral Computed Tomographic Angiography (CT Angiography)
   C. Captopril induced Radionucleotide Scan (Captopril Renogram)
   D. Duplex Doppler Ultrasonography

187. Most common cause of renal artery stenosis in young adults in India is: *(AIIMS Dec 97)*
   A. Atherosclerosis
   B. Non specific aorto-arteritis
   C. Fibro muscular dysplasia
   D. None of the above

188. Renal artery stenosis may occur in all of the following except: *(AI 2006)*
   A. Atherosclerosis
   B. Fibromuscular dysplasia
   C. Takayasu's arteritis
   D. Polyarteritis nodosa

189. A 20 year old female presents with a blood pressure of 160/110 mm Hg. Clinical examination reveals a bruit in both flanks. Which of the following statements about this patient is not true (select one option) *(PGI 09)*
   A. Enalapril may deteriorate renal function
   B. Most definitive diagnostic procedure is contrast enhanced angiography
   C. Condition is nearly always bilateral
   D. Surgical intervention may be used
   E. Fibromuscular dysplasia is the likely cause in this patient

## Renal Vein Thrombosis

190. Renal vein thrombosis is most commonly associated with : *(AI 2002)*
   A. Diabetic nephropathy
   B. Membranous glomerulopathy
   C. Minimal change disease
   D. Mesangio-proliferative glomerulonephritis

191. Renal vein thrombosis (RVT) may be seen in :
   A. Trauma *(PGI 2009)*
   B. Renal Cell Ca
   C. Pregnancy
   D. Nephrotic Syndrome
   E. Dehydration

192. Renal vein thrombosis is most commonly associated with: *(AI 2001)*
   A. Diabetic nephropathy
   B. Membranous glomerulopathy
   C. Minimal change disease
   D. Membrano-proliferative glomerulonephritis

193. All of the following are causes of Renal Vein Thrombosis, Except: *(PGI Dec 01)*
   A. Membranous Nephropathy
   B. Membranoproliferative glomerulonephritis
   C. Lupus Nephritis
   D. Renal Amyloidosis
   E. Post streptococcal Glomerulonephritis (PSGN)

194. A 10 year old child develops hematuria after 2 days of diarhoea. Blood film shows fragmented RBCs & thrombocytopenia. Ultrasound shows marked enlargement of both kidneys. The likely diagnosis is:
   A. Acute pyelonephritis *(AIIMS June 99)*
   B. Disseminated intravascular coagulopathy
   C. Haemolytic uremic syndrome
   D. Renal vein thrombosis

## Nephrolithiasis and Nephrocalcinosis

### Nephrolithiasis (Renal/Ureteric Stones)

195. All of the following statement about Renal Calculi are true, Except: *(AI 1993)*
   A. Cystine stones form in acidic urine
   B. Struvite stones form in alkaline urine
   C. Oxalate stones are radiopaque
   D. Uric acid stones are resistant to ESWL

196. Stone which is resistant to lithotripsy:
   A. Calcium oxalate *(AIIMS May 07)*
   B. Triple phosphate stone
   C. Cystine stone
   D. Uric acid stone

197. Which of the following stones is hard to break by ESWL: *(AI 2010)*
   A. Calcium Oxalate Monohydrate
   B. Calcium Oxalate Dihydrate
   C. Uric acid
   D. Struvite

198. All of the follwing types of Renal Stones are Radiopaque, Except: *(AIIMS June 2000)*
   A. Oxalate
   B. Uric Acid
   C. Cystine
   D. Mixed

199. Renal Calculi associated with proteus infection:
   A. Uric Acid *(AI 2009)*
   B. Triple Phosphate
   C. Calcium oxalate
   D. Xanthine

200. Commonest type of Renal stone seen in cases of UTI is: *(AIIMS Nov 1997)*

A. Phosphate
B. Oxalate
C. Urate
D. Cysteine

201. Ureteric colic due to stone is caused by: *(AI 2008)*
A. Stretching of renal capsule due to back pressure
B. Increased peristalsis of ureter to overcome the obstruction
C. Irriation of intramural ureter
D. Extravasation of urine.

202. Locate the renal stone with pain radiating to medial side of thigh and perineum due to slipping of stone in males: *(AIIMS June 2000)*
A. At pelvic brim
B. Intramural opening of ureter
C. Junction of ureter and renal pelvis
D. At crossing of gonadal vessels and ureter

203. Referred pain from ureteric colic is felt in the groin due to involvement of the following nerve: *(AI 2003)*
A. Subcostal
B. Iliohypogastric
C. Ilioinguinal
D. Genitofemoral

204. A 10-mm calculus in the right lower ureter associated with proximal hydroureteronephrosis is best treated with: *(AI 2003)*
A. Extracorporeal shockwave lithotripsy
B. Antegrade percutaneous access
C. Open ureterolithotomy
D. Ureteroscopic retrieval

205. A child presents with abdominal colic and hematuria. On ultrasonography a stone 2.0 cm in diameter is seen in the renal pelvis. The next step in management of this case is - *(AIIMS Nov 2000)*
A. Pyelolithotomy
B. Nephroureterostomy
C. Conservative
D. ESWL

206. T/t used for lower ureteric stone is: *(AIIMS June 98)*
A. Endoscopic removal
B. Diuretics
C. Drug dissolution
D. Laser

207. Chandu, a 45 yrs male shows calcification on the Rt side of his abdomen in an AP view. In lateral view the calcification is seen to overlie the spine. Most likely diagnosis is: *(AI 2001)*
A. Gallstones
B. Calcified mesenteric nodes
C. Renal stones
D. Calcified rib

## Nephrocalcinosis

208. Nephrocalcinosis is seen in all except– *(AIIMS May 07)*
A. Sarcoidosis
B. Distal RTA
C. Milk alkali syndrome
D. Medullary cystic kidney

209. Nephrocalcinosis is a feature of A/E: *(PGI June 2000)*
A. Primary hyperparathyroidism
B. Medullary sponge kidney
C. Vitamin D intoxication
D. Pseudo hypoparathyroidism

210. Nephrocalcinosis is seen in (select two options):
A. Medullary sponge disease *(PGI Dec 05)*
B. Acute pyelonephritis
C. Acute glomerulonephritis
D. Chronic pyelonephritis
E. Hyper parathyroidism

211. A patient is known to have calcium nephrocalcinosis for the post 10 years. All of the following dietary recommendations should be suggested, Except:
A. Protein Restriction *(AIIMS Nov 2010)*
B. Calcium Restriction
C. Salt Restriction
D. All of the above

## Congenital Diseases of the Kidney

212. Adult polycystic kidney is inherited as :
A. Autosomal-co-dominant *(AI 1997)*
B. Autosomal dominant
C. Autosomal recessive
D. X-linked dominant

213. Chromosomal location of Adult Polycystic Kidney Disease I and II respectively is: *(NBE)*
A. Chromosome 16 and 1
B. Chromosome 16 and 4
C. Chromosome 11 and 5
D. Chromosome 21 and 18

214. True about adult polycystic kidney disease is all. except: *(AIIMS 2001)*
A. Autosomal dominant inheritance
B. Hypertension is rare
C. Can be associated with cysts in liver, lungs and pancreas
D. Pyelonephritis is common

215. Which of the following is associated with adult polycystic kidney disease? *(AIIMS 2001)*
A. Berry Aneurysm in Circle of Willis
B. Saccular aneurysms of aorta
C. Fusiform aneurysms of aorta
D. Leutic aneurysms

216. Polycystic disease of the kidney may have cysts in all of the following organs *except :* *(AI 2004)*
A. Lung
B. Liver
C. Pancreas
D. Spleen

217. Which of the following is the common extrarenal involvement in autosomal dominant polycystic kidney disease – *(AIIMS Nov 04)*
A. Mitral valve prolapse
B. Hepatic cysts
C. Splenic cysts
D. Colonic diverticulosis

218. Which one of the following statements is wrong regarding adult polycystic kidney disease
A. Kidneys are enlarged in size *(AIIMS May 04)*
B. The presentation is unilateral
C. Intracranial aneurysms may be associated
D. Typically manifests in the 3rd decade

219. All of the following are true about Childhood Polycystic Kidney Disease, Except. *(AI 2009)*
A. Autosomal Dominant
B. Pulmonary Hypoplasia may be seen
C. Renal cysts are present at birth
D. Congenital Hepatic fibrosis may be seen

220. Which of the following is the most common renal cystic disease in infants is? *(AI 2005)*
A. Polycystic kidney.
B. Simple renal cyst.
C. Unilateral renal dysplasia.
D. Calyceal cyst.

221. A 12- year –old boy is referred for evaluation of nocturnal enuresis and short stature. The blood pressure is normal. The blood urea is 112 mg/dl, creatinine 6 mg/dl, sodium 119 mEq/1, potassium 4 mEq/1, calcium 7mg/dl, phosphate 6mg/dl and alkaline phosphatase 400 U/l.Urinalysis shows trace proteinuria with hyaline casts; no red and white cells are seen. Ultrasound shows bilateral small kidneys and the micturating cystourethrogram is normal. The most likely diagnosis is: *(AIIMS Nov 03)*
A. Alport's syndrome
B. Medullary sponge kidney
C. Chronic glomerulonephritis
D. Nephronophthisis

222. An 8 year old child suffering from recurrent attacks of polyurea since childhood presents to the paediatrics OPD. On examination the child is short statured. Vitals and B.P. are normal. Serum Creatinine – 6 mg%, HCO3 – 16 meg, Na-134, $K^+$ 4.2. On USG bilateral small kidneys are seen. Diagnosis is – *(AIIMS May 01)*
A. Reflux Nephropathy
B. Nephronophthisis
C. Polycystic kidney disease
D. Medullary cystic kidney disease

223. Medullary cystic disease of the kidney is best diagnosed by: *(AI 2002)*
A. Ultrasound
B. Nuclear scan
C. Urography
D. Biopsy

224. The most common cause of renal scarring in a 3 year old child is: *(AI 2005)*
A. Trauma.
B. Tuberculosis.
C. Vesicoureteral reflux induced pyelonephritis.
D. Interstitial nephritis.

225. The neonatal kidney achieves concentrating ability equivalent to adult's kidney by: *(AI 2004)*
A. One year of age
B. Eighteen months of age
C. Three to six months of age
D. Just before puberty

## Renal Tumours

### Renal Cell Carcinoma (RCC)

226. The most common histological variant of renal cell carcinoma is: *(AIIMS Nov 2005)*
A. Clear cell type
B. Chromophobe type
C. Papillary type
D. Tubular type

227. Chromophobe variant of Renal cell carcinoma is associated with : *(AI 2010)*
A. VHL gene mutations
B. Trisomy of 7 and 17 (+7, +17)
C. 3 p deletions (3p-)
D. Monosomy of 1 and Y (-1, -Y)

228. A 40 year old man presented with painless hematuria Bimanual examination revealed a ballotable mass over the right flank. Subsequently right nephrectomy was done and mass was seen to be composed of cells with clear cytoplasm. Areas of hemorrhage and necrosis were frequent. Cytogenic analysis of this mass is likely to reveal an abnormality of:
A. Chromosome 1 *(AI 2004)*
B. Chromosome 3
C. Chromosome 11
D. Chromosome 17

229. Which of the following statement about Renal Cell Carcinoma (Hypernephroma) is false: *(AIIMS Nov 93)*
A. Originate in the cortex
B. Histologically are usually Adenocarcinomas
C. May present with varicocele
D. Radiosensitive

230. Not correct regarding Renal cell carcinoma:
A. May be associated with varicocele
B. May invade renal vein *(AIIMS Dec 94)*
C. More common in female
D. Arises from proximal convoluted tubule

231. Classic triad inRenal cell carcinoma includes all of the following, Except: *(AI 1991)*
A. Hematuria
B. Hypertension
C. Flank mass
D. Abdominal Pain

232. All can be seen in hypernephroma, Except:
   A. Polycythemia *(AIIMS Nov 93)*
   B. Renal vein thrombosis
   C. Hypertension
   D. Hematuria

233. Paraneoplastic syndroime associated with RCC are all of the following except: *(AI 2009)*
   A. Polycythemia
   B. Hypercalcemia
   C. Malignant hypertension
   D. Cushing syndrome

234. Most common site for secondary metastasis in a case of Hypernephroma: *(AIIMS Feb 1997)*
   A. Adrenal
   B. Lungs
   C. Brain
   D. Bones

235. A pt. presented with renal cell carcinoma invadving IVC and the renal vein. False statement is: *(NBE)*
   A. Preop biopsy is not necessary
   B. IVC involvement indicates inoperability
   C. Pre op radiotherapy is not essential
   D. Chest x-ray should be done to rule out pulmonary metastasis.

## Wilm's Tumor

236. All are associated with Wilm's tumor except: one:
   A. Anirida *(AIIMS Feb 1997)*
   B. Male pseudohermaphrodite
   C. Arthogryposis multiplex congenital
   D. Hemihypertrophy

237. Commonest presentation of Wilm's Tumor is:
   A. Hematuria *(AIIMS Nov 95)*
   B. Abdominallump
   C. Hydronephrosis
   D. Pain in abdomen

238. Whichof the following statements about Wilm's tumor is true: *(AIIMS Nov 92)*
   A. Always Unilateral
   B. Associated with poor prognosis
   C. Most common site of metastasis is bone
   D. Radiosensitive

239. The most important determinant of prognosis in Wilms tumor: *(AI 2006)*
   A. Stage of disease
   B. Loss of heterozygosity of chromsome 1p
   C. Histology
   D. Age less than one year at presentation

240. Which of the following is the Post – Chemotherapy based staging system in Wilm's tumor: *(AI 2009)*
   A. National Wilm's Tumor staging System (NWTSG)
   B. International Society of Pediatric Oncology (SIOP)
   C. AJCC TNM
   D. Chadwick

## Hepatorenal Syndrome

241. Features of Hepatorenal syndrome are (select two options): *(PGI June 06)*
   A. Urine sodium < 10 meq/l
   B. Normal renal histology
   C. Renal function abnormal even after liver become normal
   D. Proteinuria < 500 mg/day

242. Which of the following statements is incorrect with regard to Hepatorenal syndrome in a patient with cirrhosis
   A. Createnine clearance < 40 ml/min *(AI 2003)*
   B. Urinary sodium < 10mq/L
   C. Urine osmolality lower than plasma osmolality
   D. No sustained improvement in renal function after volume expansion.

243. Which of the following statements is incorrect with regard to heptorenal syndrome in a patient with cirrhosis
   A. The creatinine clearance is > 40 ml/min
   B. The urinary sodium is less than 10 mmol/L
   C. The urine osmolality is lower than the plasma osmolality *(AIIMS Nov 2004)*
   D. There is poor response to volume expansion

## Rhabdomyolysis

244. A 28 year old boy met with on accident and sustained severe crush injury. He is most likely to develop:
   A. Acute Renal Failure *(AIIMS Nov 09)*
   B. Hypophosphatemia
   C. Hypercalcemia
   D. Acute Myocardial Infarction

245. All of the following are causes of Rhabdomyolysis, Except: *(PGI June 99)*
   A. Cocaine Intoxication
   B. Hyperphosphatemia
   C. Hypokalemia
   D. Crush injury

246. Rhabdomyolysis and Myoglobinuria may be seen in:
   A. Viperbite *(PGI June 02)*
   B. Multiple Hornet Stings
   C. Clostridium Perfringes
   D. Streptococcus
   E. All of the above

247. All of the following are causes of Rhabdomyolysis and myoglobinuria, Except: *(PGI Dec 06)*
   A. Hyperpyrexia
   B. Viper snake venom
   C. Hyperthyroidism
   D. Multiple Hornet Stings
   E. All of the above

248. All of the following are true about Rhabdomyolysis, Except: *(PGI Dec 04)*
   A. Hyperuricemia
   B. Hyperphosphatemia
   C. Hypercalcemia
   D. ↑ Creatine kinase

249. Features of Rhabdomyolysis include all of the following, Except: *(PGI Dec 04)*
A. Acute muscular weakness
B. Myoglobinuria
C. Hemoglobinuria
D. Acute Renal Failure

## Tumor Lysis Syndrome

250. Tumor lysis syndrome is associated with all of the following laboratory feature except:
A. Hyperkalemia *(NBE)*
B. Hypercalcemia
C. Hyperuricemia
D. Hyperphosphatemia

251. All of the following are seen in Tumor Lysis Syndrome, except: *(NBE)*
A. Hyperkalemia
B. Hypercalcemia
C. Hyperuricemia
D. Hyperphosphatemia

252. Test used to predict prognosis for return of renal function a patient with tumour lysis syndrome is:
A. Serum creatinine *(NBE)*
B. Serum phosphate
C. Serum potassium
D. Serum Uric acid

## Bartter's Syndrome and Gitelman's Syndrome

253. In Barter's syndrome, what is seen- *(NBE)*
A. Metabolic acidosis
B. Hypokalemia
C. Hyperkalemia
D. Decrease in urinary calcium

254. All of the following statements about Bartter Syndrome and Gitelman's Syndrome are true, except: *(NBE)*
A. Autosomal Recessive Inheritance
B. Bartter Syndrome Presents earlier in life than Gitelman's Syndrome
C. Genetic defect in Bartter Syndrome involves the transport proteins in the distal tubule
D. Hypercalciuria is more common in Bartter Syndrome

255. An adolescent male presents with Hypokalemia, Metabolic Alkalosis, Hypercalciuria and Nephrocalcinosis. His Blood Pressure is normal. The likely diagnosis is: *(NBE)*
A. Bartter Syndrome
B. Gitelman's Syndrome
C. Liddle's Syndrome
D. Renal Tubular Acidosis

256. All of the following are features of Bartter's syndrome, Except: *(NBE)*
A. Hypokalemia
B. Hypermagnesemia
C. Hyperprostaglaridine
D. Hyper calciurea

## Contrast Induced Nephropathy (CIN)

257. Which of the following is the most important strategy to prevent contrast nephropathy: *(NBE)*
A. Fenoldopam
B. N-Acetylcysteine
C. Hydration with normal saline
D. Hemodialysis

258. All of the following pharmacological agents may be used for reducing risk of contrast nephropathy, except: *(NBE)*
A. Fenoldopam
B. N-Acetylcysteine
C. Prostaglandins
D. Furosemide

259. All of the following are strategies to prevent contrast nephropathy, except: *(NBE)*
A. Intravenous Hydration
B. Use of High Osmolar Contrast Agents
C. Theophylline administration
D. Hemodialysis

## Miscellaneous

260. A 65 year old male smoker presents with gross total painless hematuria. The most likely diagnosis is:
A. Carcinoma of urinary bladder *(AI 2003)*
B. Benign prostatic hyperplasia
C. Carcinoma prostate
D. Cystolithiasis

261. An elderly male presents with one episode of gross haematuria. All of the following investigations are recommended for investigating this patient except:
A. Cystoscopy *(AI 2007)*
B. Urine microscopy for malignant cells
C. Urine tumor markers
D. Intravenous Pyelogram

262. A 60 yr old smoker came with a history of painless gross hematuria for one day. Most logical investigation would be: *(AI 2007)*
A. Urine routine
B. Plain X ray KUB
C. USG KUB
D. Urine microscopy for malignant cytology

263. A seven year old asymptomatic girl is found to have persistant hypertension. There is no significant history and urine examination is normal. Which of the following is the most likely cause: *(AI 2010)*
A. Essential Hypertension
B. Renal Parenchymal Disease
C. Polycystic Kidney Disease
D. Coarctation of Aorta

264. A child presented with intermittent episodes of left sided flank pain. Ultrasonography reveals a large hydronephrosis with dilated renal pelvis and cortical thinning with a normal ureter. Kidney differential function was observed to be 19% which of the following is the best management: *(AI 2010)*
   A. Nephrectomy
   B. Pyeloplasty
   C. External Drainage
   D. Endopylostomy

265. Not a cause of granular contracted kidney-
   A. Diabetes mellitis *(AIIMS Dec 94)*
   B. Chronic pyelonephritis
   C. Benign nephrosclerosis
   D. Chronic glomerulonephritis

266. All of the following are causes of granular contracted kidney except: *(AI 1997)*
   A. Benign nephrosclerosis
   B. Chronic pylonephritis
   C. Diabetes mellitus
   D. Chronic glomerulonephritis

267. Urinary $K^+$ excretion is increased in: *(AIIMS Nov-04)*
   A. Bronchiectasis
   B. Meningitis
   C. Osteomyelitis
   D. Hepatitis

268. Renal damage due to amphotericin B are all, *except*
   A. Azotemia *(AIIMS Nov 01)*
   B. Renal tubular acidosis
   C. Glomerulonephritis
   D. Hypokalemia

269. Which of the following drugs is not a part of the 'Triple Therapy' immunosuppression for post-renal transplant patients? *(AI 2006)*
   A. Cyclosporine
   B. Azathioprine
   C. FK 506
   D. Prednisolone

270. Most common presentation of Renal Tuberculosis is: *(NBE)*
   A. Renal colic
   B. Sterile Pyuria
   C. Intractable urgency
   D. Painful micturition

## ANSWERS, REFERENCES, EXPLANATIONS AND RELEVANT HIGH YIELD FACTS

### Urinalysis

**1. Answer is A (Kidney):** *Chandrasoma Taylor 2nd/ 127; Harrison 16th /251, 248; Harrison 17th/ 270-273, 1758 Harrison 18th/p 336-339, 2301*

***RBC casts are suggestive of glomerular (Kidney) injury.***

**Urinary casts** are formed when proteins and other organic matter solidify in the renal tubule. The presence of casts in urine is indicative of disease of the nephron.

**Casts may contain:**

| *Proteins* | *Erythrocytes* | *Leucocytes* | *Epethelial cells* |
|---|---|---|---|
| Hyaline casts | Red cell casts | WBC cast | Epithelial casts |

**Clinical significance of different casts:**

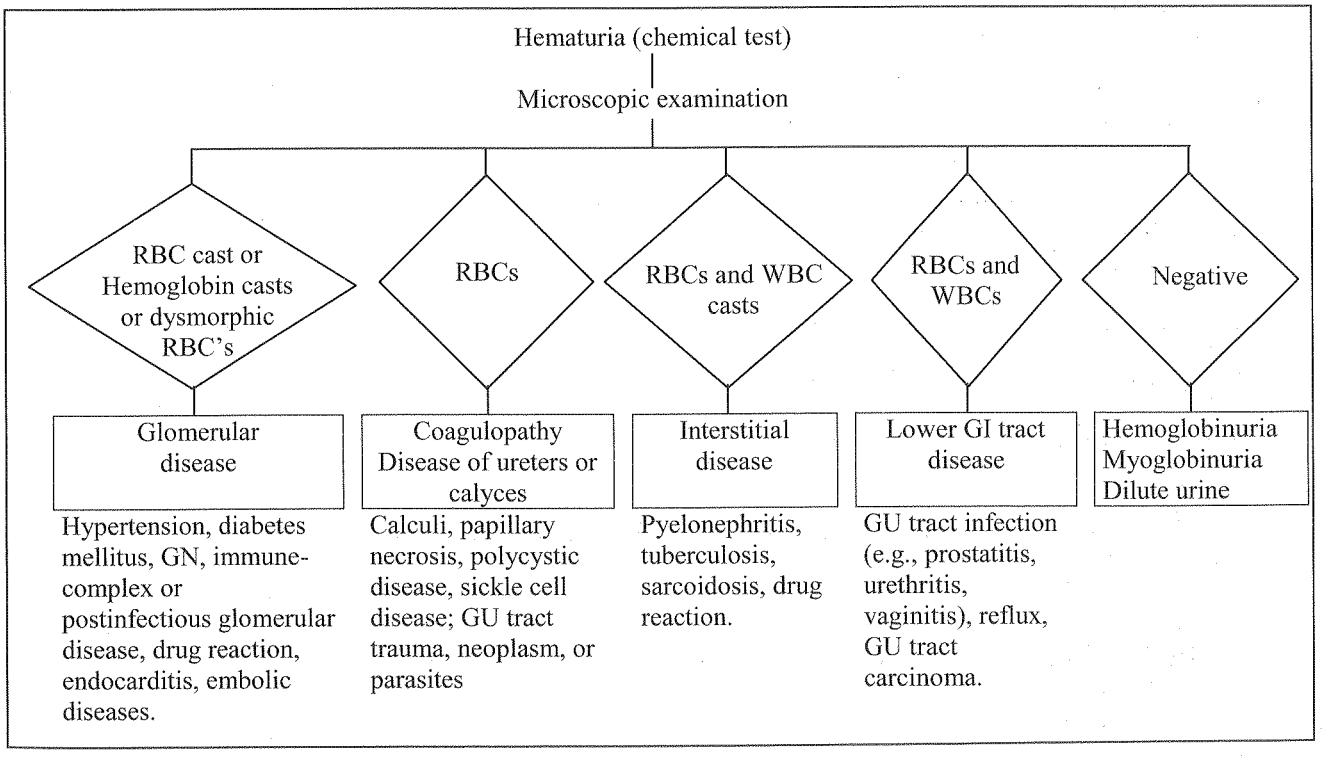
| | |
|---|---|
| a. ***Hyaline casts*** : | • This is a *normal constituent* Q of urine and has *no attached significance* Q.<br>• *Tom Horsfall protein* Q is protein *secreted by epithelial cells of loop of henle* Q.<br>• *This protein may be excreted as Hyaline cast.* Q |
| b. ***RBC cast*** : | • are suggestive of *glomerular injury* Q. |
| c. ***White cell casts*** : | • are suggestive of *interstitial injury* and may be seen in *interstitial nephritis* Q. *WBC cast with bacteria indicate pyelonephritis* Q. |
| d. ***Broad granular casts*** : | • are *seen in CRF* Q and suggests interstitial fibrosis and dilatation of tubules. |
| e. ***Pigmented muddy brown granular casts*** : | • are suggestive of *ischaemic or nephrotoxic injury* Q i.e. *Tubular Necrosis* Q. |

**2. Answer is B (20% Dysmorphic RBC) :** *Harrison 18th/p 339, 340 Harrison 17th/272, 273 Harrison 16th/251*

***Presence of Dysmorphic RBC's cast suggests hematuria of glomerular origin.***

*Presence of Bright Red RBC's and 100 RBC per HPG suggest gross hematuria but do not indicate glomerular origin of hematuria.*

*Presence of $\beta_2$ microgloobulin in urine indicates tubular injury and not glomerular injury.*



3. **Answer is A and E (Dysmorphic R.B.C and R.B.C. cast):** *Harrison 18th/p 339 Harrisons 17th/ 272, 273; 16th/251; Refer previous question*

*Presence of Dysmorphic RBC and RBC cast suggests hematuria of glomerular origin or a glomerular disease.*

4. **Answer is B (20% Dysmorphic RBC's):** *Harrison 15th/267; 16th/251; Harrison 17th/ 273 Harrison 18th/p 339*

*'The RBC's of Glomerular origin are often Dysmorphic* ***when examined by Phase contrast microscopy'. 'Hematuria with Dysmorphic RBC's cast and protein excretion > 500 mg/d is virtually diagnostic of Glomerulonephritis.'***

*- Harrisons 17th/273*

5. **Answer is B (Acanthocytes):** *Harrison 15th/ 681; 16th/615; Harrison 17th/ 652, 1786 Harrison 18th/p 2340, 2301*

***Acanthocytes are erythrocytes characterized by multiple spiny cytoplasmic protections (spur cells).***
*These are seen as a consequence of abnormal lipid metabolism such as in severe liver disease and are not a feature of glomerular (renal disease).*
*Haematuria with dysmorphic RBC's cast are a characteristic feature of glomeulonephritis.*
*(crenated RBC are a type of dysmorphic RBC's).*

6. **Answer is A and B (Alports's syndrome and IgA nephrotpathy):** *Nelsons 18th/2169, 2170-2173; Rudolph Pediatrics 21st /1682*

*Alports's syndrome and IgA nephropathy are characterized by recurrent episodes of gross hematuria.*

***Recurrent episodes of gross haematuria***
*Recurrent Gross Haematuria should be distinguished from isolated episodes of gross hematuria, as it is a charachteristic feature of some specific disorders*

| *Charachteristic Causes of Recurrent Gross Haematuria (Nelson 18th/2169)* | |
|---|---|
| *1. IgA Nephropathy*<br>*2. Alports syndrome*<br>*3. Thin Glomerular basement membrane disease*<br>*4. Hypercalciuria*<br>*5. Urolithiasis* | *Isolated Glomerular diseases with recurrent Gross haematuria* |

*Recurrent Gross Haematuria must be distinguished from Urethrorrhagea.*
*Urethrorrhagia refers to urethral bleeding in the absence of urine.It is associated with dysuria and blood spots on underwear after voiding .It often occurs in prepubertal boys at intervals, several months apart over a period of many years, and has a benign self limiting cause.*

7. **Answer is C (Broad Cast):** *Harrison 16th/251; Harrison 17th/ 273, 1758 Harrison 18th/p 339, 340*

*Broad casts are characteristic of Chronic Renal failure.*
**Broad Casts :** arise in the dilated tubules of enlarged nephrons, that have undergone compensatory hypertrophy in response to reduced renal mass i.e. chronic renal failure.
**Waxy casts :** are degenerated cellular casts seen in urine of patients with chronic renal failure.

8. **Answer is B (Coarse granular casts):** *CMDT 2002/ 920; 2009/795 (table); Harrison 16th/248; Harrison 17th/ 273 Harrison 18th/p 339*

***'Renal tubular casts' are characteristic of Acute tubular disease and interstitial nephritis*** *but are not provided amongst the options. Coarse granular casts though non specific, can represent acute tubular necrosis and thus are the single best answer amongst the options provided. Muddy brown granular casts are characteristic of acute tubular necrosis.*

- **Hyaline casts** as explained earlier are normal constituents of urine and may be found in
  - Concentrated urine
  - Febrile disease

- After strenuous exercise
- In the course of diuretic therapy

They are thus not indicative of any form of renal disease.

- **White cell casts** indicate an interstitial type of renal disease such as interstitial nephritis and infective diseases like pyelonephritis but not a renal tubular disease.
- **Cystein oxalate cell casts** are specific entities present only when excretion of these are raised and do not indicate a tubular disorder.

9. **Answer is A (W.B.C):** *Harrisons 16th/251, 248, 17th/ 272, 273, Harrison 18th/p 339 Chandrasoma Taylor 2nd/127*

*Presence of W.B.C cast in urine of patients with suspected pyelonephritis is considered pathognomic.*

*'Leucocyte casts (W.B.C cast) are present in the urine of some patients with Pylonephritis and the detection of these is considered pathognomic' – Harrisons 16th/1717*

10. **Answer is C (Organisms in excess of 100,000 (CFU/ml):** *Heptinstall's Pathology of the kidney 6th/994; Diagnosis of Genitourinary disease by Resnick and Older 2nd /275, 276, 277*

***Although acute pyelonephritis is usually associated with organisms in excess of 100,000 CFU/ml, this test cannot be utilized to localize the infection to kidney as such high counts may well be seen in cases of uncomplicated infections of the lower urinary tract.***

- ***White Blood cell casts :***
  'Presence of white blood cell casts in urine suggest that inflammation is taking in the kidney itself' - Heptinstall
  'Leucocyte casts (WBC casts) are present in urine of some patients with Acute pyelonephritis and the detection of these casts is pathognomic' – Harrisons 16th/1717
- ***Antibody to Tomm Horsfall Protein***
  *Tomm Horsfall protein is exclusively produced by cells in the ascending limb of loop of Henle and is normally found in urine.* In conditions such as pyelonephritis *(secondary to conditions such as obstructive renal disease or severe vesico- uretric reflux)* this protein gets deposited in renal interstitium and bowman's space where it stimulates antibody fermation. **Antibodies to Tomm Horsfall proteins suggest infection of the upper renal tract (pyelonephritis) - Diagnosis of Genitourinary disease**
- ***Tests for impaiment of concentrations of urine*** may be used to differentiates acute pyelonephritis and infection confined to lower urinary tract – Heptinstall

Test to localize bacteria to Kidney (Pyelonephritis)
(Complicated vs Uncomplicated UTI)

| Invasive (Gold standard) | Non Invasive tests (Suggestive) |
|---|---|
| Bacterial growth in urine collected by direct ureteral catheterization | • ***White blood cell casts in urine***<br>• ***Raised serum antibody levels to Tomm Horsfall proteins***<br>• Elevated levels of beta – 2 microglobulins in urine<br>• Urinary enzyme estimation for LDH<br>• The presence of antibody coated organisms in urine<br>• Raised serum levels of C reactive proteins<br>• ***Determination of maximum urinary concentrating ability***<br>• **Imaging tests:** USG, IVU, DMSA, CTscan<br>*'The DMSA scintography provides the most reliable test at the present time for the diagnosis of acute Pyelonephritis'* |

11. **Answer is A (Proteinuria >3.0 – 3.5 g/day):** *'Manual of Nephrology 7th/141, 142; Diseases of Kidney and Urinary Tract 8th/317, 318*

*Nephrotic range proteinuria (> 3.0 – 3.5 g/day) is characteristic of Glomerular proteinuria.*

**Tomm Harsfall Protein in urine is a feature of tubular proteinuria**

Tomm Harsfall protein is synthesized in the tubular cells of ascending limb of loop of henle and distal tubule and is secreted into urine. Under conditions of tubulo interstitial injury (tubular proteinuria) increased Tomm Harsfall protein may be secreted in urine from injured tubular cells.

**Glomerular proteinuria is associated with an increase Albumin: β2 microglobulin, ratio usually > 1000:1**

| Feature | Normal value | Glomerular proteinuria | Tubular proteinuria |
|---|---|---|---|
| Albumin: β2 microglobulin ratio | Usually 50:1 to 200:1 | Usually >1000 : 1 | Usually < 10:1 |

**Glomerular proteinuria is associated with Albumin > Globulin**

*Albuminuria is the hallmark of glomerular proteinuria*

Albumin > Globulin

| Feature | Glomerular Proteinuria | Tubular proteinuria |
|---|---|---|
| Pathology | Defect in glomerular filtration barrier resulting in increased filtration of normal proteins | Defect in tubular reabsorption resulting from damage to renal tubulointestitial region |
| Total protein excretion per day | Usually > 2.0 g/day<br>Proteinuria may reach nephrotic range > 3.5 g/day | Usually < 2.0 g/day<br>Proteinuria never reaches nephrotic range. |
| Protein type | • *Albuminuria is the hallmark of Glomerular proteinuria.*<br>• **Proteinuria chiefly consists of albumin**<br>• Other low molecular weight proteins, may be present<br>• Globulin may be present when proteinuria is not selective.<br>• **Albumin is usually greater than globulins** (Albumin >Globulin) | • *Low molecular weight proteinuria is the hallmark of tubular proteinuria.*<br>• Proteinuria chiefly consists of Low molecular weight proteins (alpha and beta microglobulins). Albumin is invariably present<br>• Albumin is invariably present |
| Albumin/ β2 microglobulin ratio | • Albumin is significantly greater than other low molecular weight proteins eg. β2 microglobulin<br>• Albumin :β2 microglobulin ratio usually exceeds 1000:1 | • Albumin microglobulin ratio is reduced as increased amount of β2 microglobulin is excreted.<br>• Albumin: β2 microglobulin ratio is usually less than 10:1 |
| Tomm Harsfall Protein | Tomm Harsfall proteins are not increased as there is no injury to tubular cells | Tomm Harsfall protein secretion may be increased by injured tubular cells of ascending loop of henle & distal tubule. |
| • N Acetyl glucosamine<br>• Lysozyme | Normal | May be increased<br>(Increased in case of tubular cell injury) |

**12. Answer is B (Is benign):** *Rudolph Pediatrics 21st/1664*

***Orthostatic proteinuria is believed to be benign condition and long term studies have shown that it is not associated with any renal disease.***

| Orthostatic proteinuria |
|---|
| • *Orthostatic proteinuria is defined as proteinuria occurring only in the upright position* |
| • *It is most commonly seen in children and young adults and its prevalence decreases with age* |
| • *Orthostatic proteinuria does not typically exceed 1gm/day (<1.0 gm/day)* |
| • *Orthostatic proteinuria is a benign condition and may resolve spontaneously* |
| • *Orthostatic proteinuria is not associated with increase risk of any renal disease.* |

**13. Answer is C (Gamma Globulins):** *Harrison's 16th/657; Primer on kidney diseases 4th/256; clinical Laboratory medicine 6th/350*

***Bence Jones proteins are composed of light chains of the type found in normal or pathological gamma globulins***

Bence Jones proteins: Review

- Bence Jones Proteins are abnormal proteins charachteristically found in the urine of patients with multiple myeloma (and other paraprotenemias)
- These proteins have been shown to be composed of only of immunoglobulin light chains (Normal complete immunoglobulins comprise of both heavy chains and light chains and hence Bence one Proteins are believed to represent Incompete Immunoglobulins
- Since Bence Jones proteins respresent light chains found in normal immunoglobulins, these proteins also belong to the category of gamma globulins like normal immunoglobulins
- In multiple myelma (and some other paraproteinemisa) there is excessive production of light chains over heavy chains. These light chains are eliminated in urine as Bence Jones proteins
- Bence ones proteins can be detected in urine by a charachteristic *heat coagulability test*[Q] due to their very distinctive chemical character.
  'These proteins (Bence Jones / Light chains) precipitate when heated to between 40°C and 60°C, dissoive an boiling (90°C- 100°C) and reprecipitate when cooled back to between 40°C and 60°C'

This unusual heat solubility property of Bence Jones protein is used as a screening test for the presence of urinary Bence Jones proteins.

**14. Answer is C (Mu heavy chain disease):** *Harrison's 17th/707, Refer text below*

***Bence Jones Proteinuria may be seen in 'Mu' heavy chain disease due to excretion of kappa light chains in urine***

***Bence Jones proteins (free light chains) are characteristically absent in alpha and gamma light chain diseases but may be seen in mu heavy chain disease. The presence of Bence Jones light chains in urine particularly kappa light chains is a distinguishing feature to identify mu heavy chain disease.***

*'The only features that may distinguish patients with mu heavy chain disease are the presence of vacuoles in malignant lymphocytes and excretion of* ***kappa light chains in urine*** *' – Harrison*

*'Bence Jones Protein is absent in alpha and gamma light chain diseases but has been reported in mu heavy chain disease' - Clinical Biochemistry (Churchill- Livingstone) 1st (1995) / 502*

*'Although mu chain is not found in the urine of patients with mu heavy chain disease, Bence Jones light chains are commonly (50%) found in urine particularly kappa chains. The latter while still produced in mu heavy chain disease are not assimilated because of heavy chain gene aberrancies leading to truncated forms'- Pathology and Genetics of Tumors of Haemopoetic and Lymphoid Tissue (WHO classification of Tumors) 2001/155*

***Heavy chain diseases*** *are rare lymphoplasmacytic malignancies that exclusively produce monoclonal heavy chains and no light chains. Heavy chains diseases are classified as Alpha, Gamma and Mu heavy chain diseases based on the defect in synthesis of alpha, gamma or mu heavy chains, respectively (Delta and Epsilon heavy chain diseases are extremely rare and have not been reported). The diagnosis of heavy chain diseases depends on demonstration of the specific monoclonal heavy chain in serum or tissues by electrophoresis, immunoelectrophoresis or immunofixation techniques*

**15. Answer is C ( DTPA renogram ) :** *Principles And Practice Of Paediatric Nephrology by Nammalwar and Vijay Kumar/85*

***Now the most convenient method of estimating renal function is by isotope renography***- *Nammalwar /85*

| DYNAMIC RENAL SCAN (RENOGRAM, DTPA scan or a Mag3 ) | STATIC RENAL SCAN ( DMSA SCAN) |
|---|---|
| • DTPA and Mag3 are rapidly excreted by the kidney and are therefore used as radiopharmaceutical agents for a dynamic scan<br>• The patient is given a small and simple intravenous injection and a *series of images* of the kidneys are taken immediately thereafter with the help of a gamma camera<br>- Angiographic phase<br>- Parenchymal phase<br>- Drainage phase<br>• This scan is preferred for information about the blood flow to the kidneys ,how well each kidney is functioning for the production of urine and if there is any obstructions in urine output. | • DMSA is an agent that concentrates in the renal parenchyma for a long time and is therefore used for a static scan<br>• The patient is given a small and simple injection into a vein. After *this the patient may leave but will be given a time to return about three hours later*. The patient will then be required to lie on a scanning table and images will be taken with the help of a gamma camera.<br>• This scan is preferred for information about the size, shape and position of the kidneys.<br>• The test also shows if there are there are scars on the kidney from a previous infection. |

**Remember :**

- **Renogram, MAG3 or DTPA** is primarily used to study the ***function of kidneys.***
- **Static Renal Scan ,DMSA scan** is primarily used to look at the ***structure of kidneys.***

**16. Answer is D (Radio-Renogram i.e. DTPA Scan) :** *Ghai 4th / 364 ; Bhaduri / 343*

***Radiorenogram is the next best investigation of choice.***

*The next step would be to assess Renal function and the possible site of obstruction if that is the cause for anuria.*
*The choice lies between an IVP or a Radio-Renogram. Out of these two a Radio Renogram is a distinctly better option.*
*Imaging of the kidney and urinary tract have been greatly simplified by introduction of Radio nucleotide methods.*
*These are now fast Replacing radiocontrast studies like IVP.*
*Radionucleotide procedures are non invasive, highly sensitive and expose patients to less radiation.*

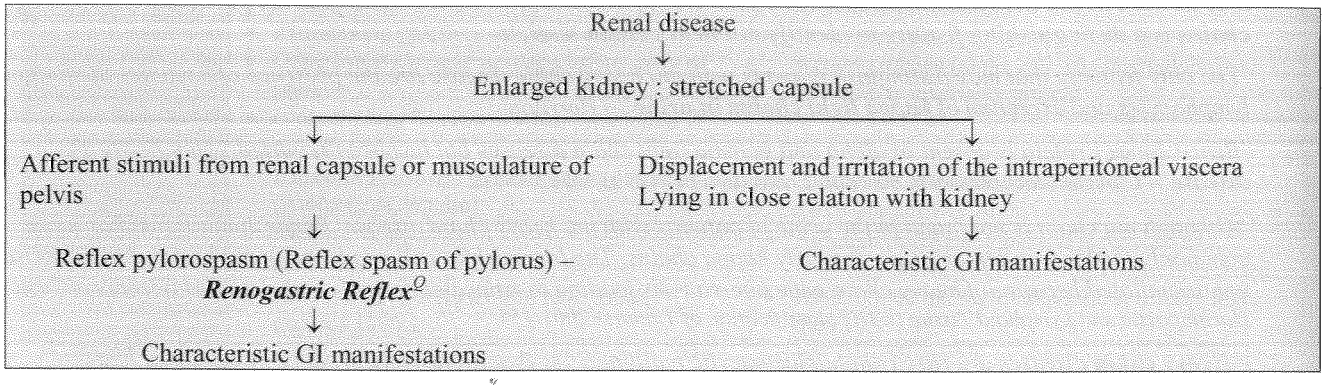
**17. Answer is B (DTPA scan):** *Repeat; Refer previous question*

***The next step would be to assess Renal function which is best achieved by DTPA scan amongst the options provided.***

**18. Answer is B (Renogastric Reflex):** *S. Das Surgery 4th/ 410*

***Afferent stimuli from renal capsule or musculature of pelvis may produce reflex spasm of the pylorus through the Renogastric reflex. This explains GI symptoms in Renal disease.***

Renal disease often presents with various GIT manifestation such as – abdominal distension, tenderness, pain, vomiting.




**19. Answer is A (Suprapubic aspiration):** *Smiths Urology 16th/46, 47, 205; Diseases of the Kidney & Urinary tract 8th/832*

***Urine obtained from suprapubic aspiration is least likely to be contaminated***—*Diseases of the kidney & urinary tract 8th/832*

Contamination with different methods of urine collection

Sample from Urine bag > Voiding sample (Mid stream) > Sample from Urinary catheter > Sample from Suprapubic aspiration

*Suprapubic aspiration avoids potential contamination but is rarely used because of its invasiveness*
*It may be indicated in children♀ (and selected other patients)*

**Desirable properties of a voided sample**

1. It is best to collect a clean voided mid stream urine sample
   (First 15-30 ml are discarded and the next 50- 100 ml are collected)
   *The midstream clean catch method reduces the likelihood of contamination with meatal or urethral secretions*
2. Freshly voided specimen should be tested (Within one hour of voiding)
3. Urine specimen should not be collected immediately after the patient has eaten
   (Should be obtained a few hours after the patient has eaten)
4. First voided morning specimen should be obtained for qualitative protein testing
   (Patients with possible orthostatic proteinuria) and for specific gravity testing.

**20. Answer is A (E.Coli):** *Harrison 18th/ 2388*

*The most common etiological agent for Catheter Associate Urinary Tract Infection (CAUTI) is E.Coli.*

*The most common etiological agent for acute uncomplicated cystitis is E.Coli*
*The most common etiological agent for uncomplicated pyelonephritis is E.Coli*
*The most common etiological agent for Complicated UTI (e.g. CAUTI) is E.Coli*

**21. Answer is A (Quinine):** *Smith's Urology 17th/47*

***Quinine is not associated with discoloured urine.***

**Colour and Appearance of Urine**

Urine is often coloured owing to drugs and other causes

| Red Urine | Reddish Brown / Brown | Orange /yellow orange |
|---|---|---|
| • *Beet ingestion (Betacyanin excretion)*<br>• *Phenolpthaline (in Laxatives)*<br>• *Vegetable dye ingestion*<br>• *Myoglobinuria*<br>• *Haemoglobinuria*<br>• *Seoratia Marcescens bacteria can cause the Red diaper' syndrome* | • ***Nitrofurantoin*** *(Brown)*<br>• *L-Dopa*<br>• *Alpha Methyl Dopa*<br>• *Metronidazole* | • ***Rifampicin*** *(yellow orange)*<br>• ***Pyridium*** *(orange)*<br>*(Phenazopyridine)* |

**22. Answer is A (Urine output < 100 ml/hr):** *Management of Acute Kidney Problems (Springer,2010) / 473; Harrison's 18th/ Chapter 44*

*Anuria in clinical practice is defined as passage of less than 100 ml of urine in a day.*

*Oliguria is defined as a urine output 400 mL day, the minimum amount of urine that a person in a normal metabolic state needs to excrete to get rid of his or her daily solute production*

**23. Answer is A (3 or More RBC/ HPF):** *The American Urological Association (AUA) Practice Guidelines ; Standard Treatment Guidelines Urology: Ministry Of Health & Family Welfare Govt. Of India (http://clinicalestablishments.nic.in/WriteReadData/17.pdf)*

*Microscopic hematuria is defined as the presence of three or more red blood cells per high-power field on microscopic evaluation of urinary sediment from two of three properly collected urinalysis specimens.*

**24. Answer is A (White):** *Oxford Desk Reference: Nephrology (Oxford University Press) 2009/ 8*

*Chyluria is associated with passage of white coloured milk like urine.*

| Underlying condition | Possible urine coloration |
|---|---|
| • Hematuria,<br>• Hemoglobinuria,<br>• Myoglobinuria | • Pink, red , brown or black |
| • Jaundice | • Dark yellow to brown |
| • Chyluria | • White and milky |
| • Massive uric acid crystalluria | • Pink |
| • Porphyrinuria | • Red (possibly darkening upon standing or fluorescence in UV light) |
| • Alkaptonuria | • Brown to black |
| • Drugs<br>Rifampicin<br>Phenytoin<br>Chloroquine | <br>• Orange to red<br>• Red<br>• Brown |
| Triamterene<br>Methylene blue<br>Metronidazole, imipenem/cilastatin, methyldopa | • Green<br>• Blue<br>• Darkening upon standing |

| | |
|---|---|
| • Foods<br>Beetroot<br>Rhubarb, senna<br>Carotene | • Red<br>• Yellowish-brown or red<br>• Brown |

**25. Answer is C (Filariasis):** *Surgical Diseases in Tropical Countries (Jaypee) 1996/ 51;*

***The most common cause of chyluria is development of fistulous connection between the lymphatics and urinary system from occlusion and subsequent rupture of the lymphatics by filarial infection.***

*Chyluria refers to the passage of chyle in the urine and is characterized by the passage of white coloured, milk-like urine which is often aggravated by a heavy meal. It represents the development of fistulous connections between the lymphatic and the urinary system. Etiologically, Chyluria may be parasitic or nonparasitic. Parasitic chyluria is commoner in the tropics it occurs due to occlusion of the lymphatics usually from filarial infections, and rarely from other causes. Non-parasitic chyluria is rare, and typically occurs due to obstruction of the thoracic duct from various causes.*

**Causes of Chyluria**

| Parasitic diseases | Non-parasitic diseases |
|---|---|
| • ***Wuchereria bancrofti (Filariasis; Most Common)***<br>• Other Parasitic Infections (Less Common)<br>Eustorngylous gigus<br>Taenia echinococcus<br>Ascaris lumbricoides<br>Hymenolepis nana<br>Schistosoma hemotobium | • Chronic infection e.g. tuberculosis<br>• Neoplastic infiltration of retroperitoneal region<br>• Renal cell carcinoma<br>• Ureteric stone<br>• Trauma<br>• Pregnancy |

**26. Answer is A (Glomerular Filtaration):** *Essentials of Nephrology 2nd/32, 33*

***Creatinine Clearance is used to assess Glomerular function or the Glomerular Filtration Rate.***

***Creatinine*** *in serum is the end product of endogenous muscle breakdown. Creatinine is compteletely filtered by the glomerulus and neither significantly absorbed nor significantly secreted into the tubules and hence for clinical purpose creatinine clearance is the most commonly used test to assess Glomerular function.*

**Renal Function Test**

| Estimation of Glomerular Function | Estimation of tubular function | Estimation of Renal Blood Flow/ Renal Plasma Flow |
|---|---|---|
| • ***Creatinine Clearance Tests***$^{Q}$<br>• ***Inulin Clearance test***$^{Q}$<br>*(used to assess Glomerular Filtration Rate- GFR)* | • ***Water Deprivation Test***<br>*(used to assess Distal Tubular Function)* | • ***Paraaminohippurate (PAH) clearance***<br>*(used to assess Renal Plasma Flow -RPF)* |

**27. Answer is B (Creatinine Clearance):** *Diseases of Kidney and Urinary Tract 8th (Lippincott Williams) / 2059; 'Applied Physiology in Intensive Care Medicine 2nd (Springer) / 94*

***Creatinine clearance is the most accurate estimation of decline in GFR amongst the option provided.***

**Creatinine clearance is the most accurate endogenous marker for estimation of GFR to assess renal function**

- *'Assessment of GFR is the single most important test of renal function in clinical practice'* -Diseases of Kidney & Urinary Tract
- *Creatinine clearance is the most accurate* ***endogenous marker*** *for estimation of GFR to assess renal function.*

> ***Inulin*** *is an* ***exogenous marker*** *that is freely filtered by the kidneys without undergoing any metabolism, tubular secretion and /or reabsorption. Inulin is thus rapidly excreted in urine by glomerular filtration and 'Inulin clearance' has remained the Gold standard for estimation of GFR.*

- *Estimation of serum creatinine is the most widely used measure to assess renal function but is not the most accurate.*

> ***Serum creatinine is not an accurate enough measure of renal function and can be normal in initial stages of renal failure.***
>
> *'In early renal disease, however GFR can decrease substantially without changes in serum creatinine. The serum creatinine does not significantly change until the creatinine clearance is less than 70 ml/min /1.73m$^2$'.*
>
> *– The Chemotherapy Source Book 4th (Lippincott Williams) / 224*

- *Serum creatinine estimation is more accurate than estimation of serum urea or serum BUN in assessing renal function*

**28. Answer is B (Creatinine clearance may overestimate the actual GFR as renal function declines)**

*Creatinine clearance may overestimate the GFR as renal function declines, since secretion of creatinine from tubular cells is increased as renal function declines (when GFR decreases).*

*Creatinine is an endogenous metabolite that is freely filtered by the glomerulus but is also actively secreted by the proximal tubular cells into the renal tubules in very small amounts. In the steady state such 'Secretion' of creatinine into the tubules is minimal, however as GFR falls creatinine secretion is increased. Creatinine clearance thus over estimates the actual GFR especially in conditions with mild to moderate reductions in GFR.*

> ***Inulin is still considered the 'Gold standard' test for assessing GFR.***
> *Inulin clearance is more accurate than creatinine clearance as Inulin is not secreted by tubular cells.*

**29. Answer is C (Distal Tubular Function):** *Essentials of Nephrology 2nd/33*

*Water Deprivation Test is used to assess Distal Tubular Function.*

**Water Deprivation Test**

*Water deprivation test is used to assess the tubule's ability to concentrate urine. When a normal person is deprived of water, ADH secretion occurs, which acts on the* ***distal tubule and collecting ducts****, making them freely permeable to water, allowing reabsorption of water from these segments, thereby producing concentrated urine. Inability to concentrate urine during the water deprivation test thereby suggests dysfunction of distal tubules and helps to identify nephrogenic diabetes insipidus.*

## Renal Failure & Tubulointerstitial Diseases

### Acute Renal Failure:

**30. Answer is D (Rupture of Aortic Aneurysm):** *Harrison 14th/ 1505 (t); 15th/ 1546 t; 16th/1648; 17th/1753 (table 273.1); Harrison 18th/p 2294 (Table: 279-1) Renal Pathology by Craig Tisher 2nd/ 770;*

*Rupture of Aortic Aneurysm is the most unlikely cause of ATN amongst the following. It would rather result in instant death.*

**Causes of Acute Tubular Necrosis**

**Ischemic**
- *Hypovolemia* Q
- *Low cardiac output* Q
- *Renal vascular occlusion.* Q i.e. Renal vasoconstriction, DIC, Thrombotic microangiopathy (HUS, TTP, Malignant Hypertension, Vasculitis)

**Toxins**

**Endogenous Toxins**
- *Rhabdomyolysis or Crush Syndrome (myoglobins)* Q
- *Hemolysis (hemoglobins)* Q
- *Uric acid, Oxalate* Q
- *Plasma cell dyscrasias (Paraproteinemias e.g. myeloma)* Q
- *Massive burns* Q

**Exogenous Toxins**
- *Radiocontrast agents* Q
- *Cyclosporine* Q
- *Antibiotics (e.g. Aminoglycosides, Amphoterein B)* Q
- *Chemotherapy (eg. Cisplatin)* Q
- *Organic Solvents (e.g. Ethylene Glycol)* Q
- *Paracetamol* Q
- *Illegal Abortifacients*

**31. Answer is C (14th Day):** *Harrison 18th/ 2303,2306; Fluids and Electrolytes with Clinical Applications (Cengage Learning) 2008/ 428; Porth Pathophysiology: Concepts of Altered Health States/823*

***The Diuretic Phase of Acute Renal Failure typically begins 10 to14 days after the initiation of renal insult and lasts for approximately 10 days (but may last longer).***

| *Phase of Renal Failure* | *Approximate onset and Duration* |
|---|---|
| Initiation Phase | • Begins with the onset of renal insult<br>• *Lasts hours to days (usually less than 48hrs or 2 days)*<br>• *Reflects the time from the onset of the precipitating event (e.g., ischemic phase of pre-renal failure or toxin exposure until tubular injury occurs)* |
| Maintenance phase (Oliguric Phase) | • Begins after the Initiation Phase *once the renal injury becomes established*<br>• *Typically begins within 48 hours of the initiation phase and lasts for 10 to 14 days (May last longer)*<br>• During this phase the GFR and Urine output progressively decrease until they stabilize at their lowest. (GFR is may be as low as 5-10ml/min and urine output is typically <400ml/day)<br>• Fluid retention gives rise to edema, water intoxication, and pulmonary congestion if the period of oliguria is prolonged (Hypertension frequently develops during this phase)<br>• Uremic (neurologic, gastrointestinal, and cardiovascular) complications may develop during this phase<br>• ***Azotemia (Raised BUN and Creatinine) and Electrolyte imbalance typically arise during this phase.***<br>• ***Continuous Renal Replacement Therapy (CRRT) or Dialysis should be initiated in this phase.***<br>• The oliguric-anuric phase generally lasts 10 to 14 days but can last for several more.<br>• The longer the patient remains in this phase, the poorer the prognosis for a return to normal renal function |
| Diuretic Phase | • Begins after the Oliguric phase and often precedes the recovery phase<br>• *Typically begins 12 to 14 days after the initiation phase and lasts for about 10 days (May last longer)*<br>• Nephrons do not concentrate urine sufficiently to conserve electrolytes and water<br>• Loss of concentration ability leads to a gradual increase in urine output from 1-3liters or more per day up to 5-6 litres per day.<br>• Risk of dehydration and death are high<br>• BUN and serum creatinine, potassium, and phosphate levels may remain elevated or continue to rise even though urine output is increased in some cases |
| Recovery Phase | • Begins after the Diuretic Phase<br>*(Roughly 24 days after the initiation phase)*<br>• The recovery phase is the period during which repair of renal tissue takes place.<br>• Renal tubular function is progressively restored with improvement in concentrating ability.<br>• Its onset usually is heralded by a gradual return of urine output towards normal and a fall in serum creatinine, indicating that the nephrons are recovering<br>• The BUN and creatinine eventually returns to normal |

***Note: According to the more recent classification systems the Diuretic Phase is included within the Recovery phase. The diuretic phase is recognized as an event that often complicates the Recovery Phase***

**32. Answer is B (Maintenance):** *Fluids and Electrolytes with Clinical Applications (Cengage Learning) 2008/ 428; Porth Pathophysiology: Concepts of Altered Health States/823*

***Uremic complications and Electrolyte imbalance typically arise during the Maintenance Phase of Acute Renal Failure (Also known as Oliguric Phase).***

*Maintenance phase refers to the phase of Renal Failure in which the renal injury becomes established. It is also known as the Oliguric Phase. During this phase the GFR and Urine output progressively decrease until they stabilize at their lowest. Fluid retention gives rise to edema, water intoxication, and pulmonary congestion if the period of oliguria is prolonged. Hypertension frequently develops during this phase. Uremic complications and Electrolyte imbalance typically arise during this phase. Continuous Renal Replacement Therapy (CRRT) or Dialysis should be initiated in this phase. The oliguric-anuric phase generally lasts 10 to 14 days but can last for several more. The longer the patient remains in this phase, the poorer the prognosis for a return to normal renal function.*

33. **Answer is B (Maintenance) :** *Fluids and Electrolytes with Clinical Applications (Cengage Learning) 2008/ 428; Porth Pathophysiology: Concepts of Altered Health States/823*

***Continuous Renal Replacement Therapy should be initiated during the Maintenance phase (Oliguric Phase) of Acute Renal Failure.***

*Maintenance phase refers to the phase of Renal Failure in which the renal injury becomes established. It is also known as the Oliguric Phase. During this phase the GFR and Urine output progressively decrease until they stabilize at their lowest. Fluid retention gives rise to edema, water intoxication, and pulmonary congestion if the period of oliguria is prolonged. Hypertension frequently develops during this phase. Uremic complications and Electrolyte imbalance typically arise during this phase. Continuous Renal Replacement Therapy (CRRT) or Dialysis should be initiated in this phase. The oliguric-anuric phase generally lasts 10 to 14 days but can last for several more. The longer the patient remains in this phase, the poorer the prognosis for a return to normal renal function.*

34. **Answer is E (All of the above):** *Harrison 18th/2294; Harrison 17th/1753*

*All of the options provided can lead to Acute Tubular Necrosis and are listed in the table in the previous question. Abruptio placentae is an established cause of DIC and may thus cause ATN.*

35. **Answer is B (Urine sodium > 40):** *Harrison 15th/1547; 16th/1649; Harrison 17th/ 271, 1758 Harrison 18th/p 337, 2301*

*Urinary sodium excretion of more than 20mmol/L suggests intrinsic renal failure such as ATN.*

**Urine Diagnostic Indices: Differentiation of Prerenal and Intrinsic Renal failure.**

| Diagnostic index | Prerenal ARF | Intrinsic renal ARF |
|---|---|---|
| Fractional Excretion of $Na^{Q}$ (%) | <1 | >1 |
| Urine Sodium Concentration (mmol/L) $^{Q}$ | <10 mmol/L | >20 mmol/L |
| Urine Sodium concentration (meq/L)$^{Q}$ | < 20meq/L | > 40 meq/L$^{Q}$ |
| Urine Creatinine To Plasma Creatinine ratio $^{Q}$ | >40 | <20 |
| Urine specific gravity $^{Q}$ | >1.020 | ~1.010 |
| Urine osmolality $^{Q}$ (mosmol/kg $H_2O$) | > 500 | < 350 |
| Renal failure Index $^{Q}$ $U_{Na}/(U_{CR}/P_{CR})$ | <1 | >1 |
| Urine urea Nitrogen to plasma urea Nitrogen$^{Q}$ | > 8 | <3 |
| Plasma BUN/Creatinine Ratio $^{Q}$ | >20 | <10-15 |
| Urinary sediment $^{Q}$ | Hyaline Casts | Muddy Brown Granular Cast |

*Acute tubular necrosis is a cause of Intrinsic ARF.* $^{Q}$

36. **Answer is A (Prerenal Azolemia):** *Harrison 18th/p 2302 Harrisons 17th 1758; Harrisons 16th/1649*

*Fractional Excretion of $Na^+$ < 1 is a charachteristic of Prerenal Azotemia*

| Diagnostic Index | Prerenal ARF | Intrinsic Renal ARF |
|---|---|---|
| Fractional Excretion of $Na^+$ | < 1 | > 1 |

37. **Answer is A (Urinary $Na^+$ < 10 mmol/litre):** *Harrison 16th/1649; Harrison 17th/271, 1758 Harrison 18th/p337, 2302*

*Prerenal azotemia is associated with a urinary sodium excretion of less than 10 mmol/L.*

38. **Answer is C (Urinary sodium concentration > 40 meq/l):** *Harrison 18th/p 337, 2302 Harrisons 17th/271, 1758*

*Prerenal Azotemia (Prerenal ARF) is associated with a urinary sodium concentration < 20 meq/l. A urinary sodium concentration > 40 meq /l suggests intrinsic type of ARF.*

**Differentiating features between Pre-renal and Intrinsic ARF**

- Prerenal Azotemia is the most common form of ARF and is caused by renal hypoperfusion either from generalized hypovolemia or from altered renal hemodynamics resulting in hypoperfusion
- ***By definition Renal parenchymal tissue is not damaged in prerenal ARF and prerenal ARF is rapidly reversible upon correction of the primary hemodynamic abnormality***
- Analysis of urine and blood biochemistry provides several useful 'Renal failure Indices' to distinguish prerenal ARF from intrinsic ARF (Ischemic /Nephrotoxic ARF)

**Urine Diagnostic Indices: Differentiation of Prerenal and Intrinsic Renal failure.**

| Diagnostic index | Prerenal ARF | Intrinsic renal ARF |
|---|---|---|
| Fractional Excretion of Na $^{Q}$ (%) | <1 | >1 |
| Urine Sodium Concentration (mmol/L) $^{Q}$ | <10 mmol/L | >20 mmol/L |
| Urine Sodium concentration (meq/L) $^{Q}$ | < 20meq/L | > 40 meq/L $^{Q}$ |
| Urine Creatinine To Plasma Creatinine ratio $^{Q}$ | >40 | <20 |
| Urine specific gravity $^{Q}$ | >1.020 | ~1.010 |
| Urine osmolality $^{Q}$ (mosmol/kg $H_2O$) | > 500 | < 350 |
| Renal failure Index $^{Q}$ $U_{Na}/(U_{CR}/P_{CR})$ | <1 | >1 |
| Urine urea Nitrogen to plasma urea Nitrogen $^{Q}$ | > 8 | <3 |
| Plasma BUN/Creatinine Ratio $^{Q}$ | >20 | <10-15 |
| Urinary sediment $^{Q}$ | Hyaline Casts | Muddy Brown Granular Cast |

**39. Answer is C (Pre-renal failure):** *Harrison 18th/p 337, 2302 Harrisons 17th/271, 1758, 1753 (1)*

***Plasma urea / creatinine ratio of 20:1 is characteristic of prerenal ARF***
*Rhabdomyolysis and chronic glomerulonephritis are causes of Intrinsic ARF and are associated with a plasma urea / creatinine ratio of < 10-15. Ureteric calculi are associated with post-renal ARF*

| Indices | Pre-renal ARF | Intrinsic Renal ARF |
|---|---|---|
| Plasma Urea / Creatinine Ratio | > 20 | < 10-15 |

**40. Answer is C (Sodium Fraction Excretion):** *Harrison 18th/p 337, 2302 Harrison 17th/271, 1758; Harrison 16th/1649*

***Fractional Excretion of Na can distinguish Pre renal ARF from Renal ARF.***

| Indices | Prerenal ARF | Renal ARF |
|---|---|---|
| Fractional Excretion of Na ($FE_{Na}$) | < 1 | > 1 |

**41. Answer is A (20):** *Harrison 18th/p337 Harrison 17th/217; Harrison 16th/1649*
***The urinary creatinine to plasma createnine ratio in Intrinsic renal failure (Acute Tubular Necrosis) is less than 20.***

| Indices | Prerenal ARF | Renal ARF (ATN) |
|---|---|---|
| Urine creatinine/Plasma Creatinine ($U_{cr}/P_{cr}$) | >40 | <20 |

**42. Answer is D (Blood urea creatinine ratio < 20):** *Harrison 18th/p 337 Harrison 17th/271; Harrison 16th/1649*

***Intrinsic Renal Failure (ATN) is associated with a Blood Urea Creatinine ratio of <10-15 : 1. BUN creatinine ratio < 20 is thus the single best answer of choice.***

| Index | Acute Tubular Necrosis |
|---|---|
| Urine specific gravity | < 1.020 (~1.010) |
| Urine osmolality | < 350 mosmol/kg |
| Urine sodium excretion | > 20 mmol/L or > 40 meq/L |
| BUN/creatinine ratio | <10-15 : 1 |

**43. Answer is D (Plasma BUN/Creatinine ratio <20):** *Harrison 18th/337; Harrison 17th/271; Harrison 16th/1649*

***Prereanl Azotemia is characterized by Plasma BUN/creatinine ratio of >20:1***
**Oliguria (urine output <400) is a feature of prerenal Azotemia that cannot be used to differentiate Prerenal Azotemia from Intrinsic Renal failure (ATN)**

*Urine output <500 may be seen in both Prerenal and Renal Azotemia.*
*Decreased urine output represents oliguric renal failure and may be seen in both prerenal and renal azotemia.*

**Ucr/Pcr >40; $FE_{Na}$ < 1 and $U_{NA}$ < 20 meq/l are features of Prerenal Azotemia that may be used to distinguish Prerenal Azotemia from Intrinsic Renal Azotemia.**

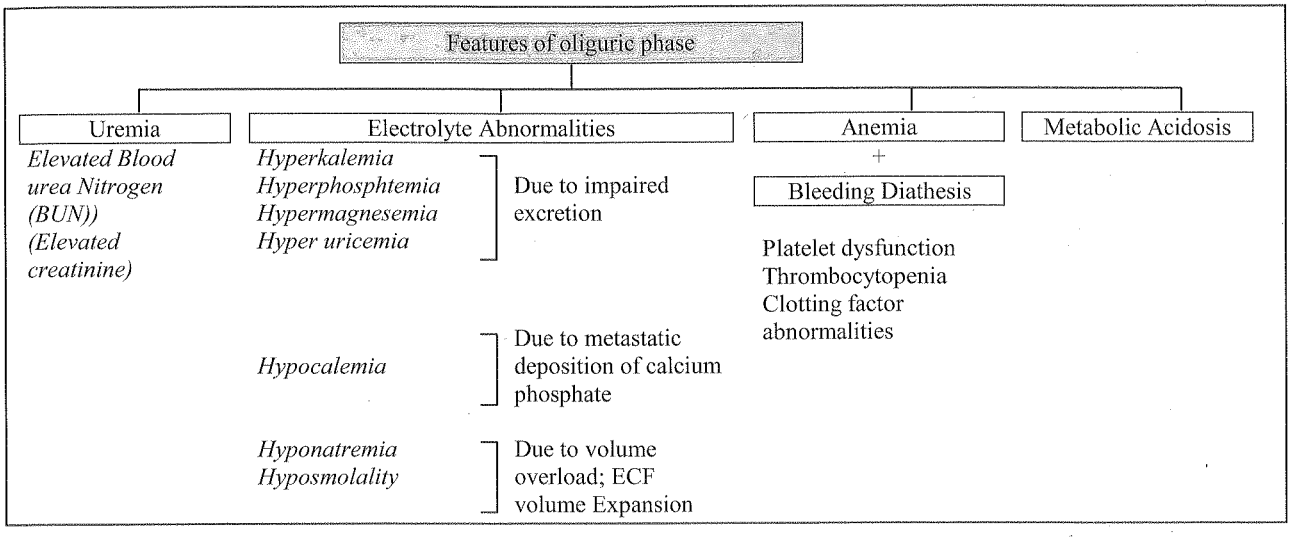
**44. Answer is A and B (urine Osmolality > 500 and sodium excretion <10 mmol/L):** *Harrison 17th/271; Harrison 16th/1649*

***Prerenal Azotemia is associated with sodium excretion <10mmol/L and a urine osmolality >500 mosmol/kg***
*Fractional excretion of Na > 1 and plasma BUN/creatinine ratio <20 favours a diagnosis of Intrinsic Renal Azotemia or ATN.*

**45. Answer is D (Hypercalcemia):** *Harrison 18th/ 2303, 2306; Harrisons 17th/1754, 1759, 1760*

***Oliguric ARF is associated with hypocalcemia and not hypercalcemia.***

*Hypocalcemia is caused by metastatic deposition of calcium phosphate, tissue resistance to PTH and reduced levels of active vitamin D.*




**46. Answer is A (Hypercalcemia):** *Harrison 18th/p 2303, 2306 Harrisons 17th/1754, 1759, 1760*

*The oliguric phase of acute renal failure is associated with hypocalcemia and not hypercalcemia*

*The oliguric phase (maintenance phase) of acute renal failure is associated with uremic and electrolyte complications. Metastatic deposition of calcium phosphate leads to hypocalcemia. Other factors that lead to hypocalcemia include tissue resistance to the actions of parathyroid hormone and reduced levels of vitamin D.*

**47. Answer is A (Hypernatremia):** *Harrison 18th/p 2303, 2306; 17th/ 1754, 1759, 1760, Refer Previous question.*

*Oliguric phase of ATN is asociated with Hyponatremia and not hypernatremia*

*Hyponatremia results from expansion of ECF volume due to dimnished water excretion and excessive administration of free water (volume overload)*

**48. Answer is A (Aminoglycoside toxicity):** *Harrison 18th /2298; Management of Acute Kidney Problems (Springer) 2010 / 321; References with Text; Pediatric Nephrology (Lippincott Williams) 2004 /1235*

***Non-Oliguric Renal Failure is typically associated with Aminoglycoside toxicity.***

*'Aminoglycoside nephrotoxicity typically is associated with non-oliguric renal failure'*

*– Management of Acute Kidney Problems*

*'Non-Oliguric renal failure is a common expression of aminoglycoside nephrotoxity and may reflect a direct inhibitory effect on solute transport along the thick ascending loop of Hence or possibly tubulointerstitial cell injury.*

*- Diseases of Kidney and Urinary Tract 8th/1035*

*'Non-Oliguric Acute Kidney Injury accompanies 10-30% of courses of aminoglycosides even when plasm levels are in therapeutic range'- Harrison 18th/ 2298*

*'The Acute Kidney Injury of Aminoglycoside toxicity is characteristically non-oliguric and reversible with a low mortality' - 'Renal and Electrolyte Disorders' by Shriev (Lippincott Williams) 2010/357-358*

| Cause of ARF | Aminoglycoside Toxicity | Contrast Associated Nephritoxicity | Glumerulonephritis | HUS |
|---|---|---|---|---|
| Urine output | *Typically Non-Oligouric* | *Oliguric more than Non-oliguric* | *Usually Oliguric* | *Usually Oliguric* |

*Non-Oliguric renal failure may also be associated with contrast induced nephropathy, however it is most typical /characteristic of Aminoglycoside toxity.*

**49. Answer is A (Acute renal failure):** *Harrison 16th / 2243, 1650; 17th/ 1759; Harrison 18th/p 2303 CMDT 2006 / 882, 881, 1230; 2009/780*

***Renal insufficiency is associated with hyperphosphatemia due to impaired renal phosphate excretion.***

- **Acute renal failure:** '*Mild Hyperphosphatemia is an almost invariable complication of Acute Renal Failure. Severe hyperphosphatemia may develop in highly catabolic patients or following rhabdomyolysis, hemolysin or tumor lysis.*' – *Harrison 16th / 1650*
- **Dibetic ketoacidosis** *or Metabolic acidosis from any other causes may be associated with hyperphosphatemia from transcellular phosphatic shifts.*

  ***However resolving phases of diabetic ketoacidosis are associated with hypophosphatemia and not hyperphosphatemia.*** *This is a result of insulin therapy for diabetic ketoacidosis.*

| Causes of hyperphosphatemia (*Harrison / CMDT*) | Causes of hypophosphatemia (*Harrison*) |
|---|---|
| Metabolic acidosis (Lactic acidosis / Diabetic Ketoacidosis) | Insulin therapy of diabetic ketoacidosis or prolonged hyperglycemia. |

| Laboratory values in DKA / Harrison 6th / 323 - 324 |
|---|
| *Phosphate values are : decreased (large changes occurs during treatment of DKA* |

*Also note that total body stores of phosphorus (Also potassium, sodium, chloride, magnesium) are reduced in DKA, but are not accurately reflected by their levels (serum values may be increased) because of dehydration and hyperglycemia. – Harrison*

- **Respiratory alkalosis** is associated with ***hypophosphatemia*** by causing intracellular shift of phosphorus into cells.

| Hypophosphatemia | Hyperphosphatemia |
|---|---|
| • Metalbolic alkalosis<br>• Respiratory alkalosis | • Metabolic acidosis<br>• Respiratory acidosis |

- **Chronic alcoholism / Alcoholism** *is known to cause* ***hypophosphatemia****. – Harrison 16th / 881*
  *Severe hypophosphatemia is common and multifactorial in alcoholic patients.*
  *Chronic alcohol use results in a decrease in the renal threshold of phosphate excretion.' – CMDT 09/780*
- **Patients with COPD and Asthma** *commonly have* ***hypophosphatemia****.*
  *This is attributed to xanthine derivatives causing shifts of phosphate intracellularly and the phosphaturic effects of beta – adrenergic agonists , loop diuretics , xanthine derivatives and corticosteroids. – CMDT 2006 / 88; 09/780*

## Chronic Renal Failure

**50. Answer is E (All of the above):** *CMDT 2008/793*

***Isothenuria and Broadcast sediment are common in chronic renal failure. Impotence and Restless legs are features of uremia seen in chronic renal failure.***

| Essentials of Diagnosis of CRF: |
|---|
| *Progressive Azotemia over months to years*<br>*Symptoms and signs of uremia when nearing endstage disease*<br>*Hypertension in the majority*<br>***Isothenuria and broad casts in urinary sediment are common***<br>*Bilateral small kidneys on ultrasound are diagnostic.* |

Symptoms and Signs of Uremia:

| Organ System | Symptoms | Signs |
|---|---|---|
| General | Fatigue, weakness | Sallow appearing, chronically ill |
| Skin | Pruritus, easy bruisability | Pallor, ecchymoses, excoriations, edema, xerosis |
| ENT | Metallic taste in mouth, epistaxis | Urinous breath |
| Eye | | Pale conjunctiva |
| Pulmonary | Shortness of breath | Rales, pleural effusion |
| Cardiovascular | Dyspnea on exertion, retrosternal pain on inspiration (pericarditis) | Hypertension, cardiomegaly, friction rub |
| Gastrointestinal | Anorexia, nausea, vomiting, hiccups | |
| Genitourinary | Nocturia, ***impotence*** | ***Isosthenuria*** |
| Neuromuscular | ***Restless legs,*** numbness and cramps in legs | |
| Neurologic | Generalized irritability and inability to concentrate, decreased libido. | Stupor, asterixis, myoclonus, peripheral neuropathy |

**51. Answer is B (Stage II):** *Harrison 18th /2319*

***Kidney damage with mild decrease in GFR is classified as stage II of chronic Kidney Disease.***

| Clinical Action Plan | | | |
|---|---|---|---|
| **Stage** | **Description** | **GFR, mL/min per 1.73 $m^2$** | **Action** |
| *1* | *Kidney damage with normal or ↑GFR* | 90 | Diagnosis and treatment, treatment of comorbid conditions, slowing progression, cardiovascular disease (CVD) risk reduction |
| *2* | ***Kidney damage with mild ↓GFR*** | 60–89 | Estimating progression |
| *3* | *Moderate ↓GFR* | 30–59 | Evaluating and treating complications |
| *4* | *Severe ↓GFR* | 15–29 | Preparation for kidney replacement therapy |
| *5* | *Kidney failure* | <15 (or dialysis) | Kidney replacement (if uremia present) |

**52. Answer is B (20-50% of Normal):** *Robbins 8th/ 907*

*Azotemia appears in the stage of Renal Insufficiency when the residual renal function (Residual GFR) is between 20 to 50 percent of normal.*

| Pathological Stage | % Reduction in GFR | Comments |
|---|---|---|
| ***Diminished Renal Reserve*** | ***50 -80*** ***(Percent of normal)*** | • *The GFR is about 50% of normal.*<br>• *Serum BUN and creatinine values are normal*<br>• *Patients are asymptomatic.*<br>*(However, they are more susceptible to developing azotemia with an additional renal insult)* |
| ***Renal Insufficiency*** | ***20 to 50*** ***(Percent of normal)*** | • *The GFR is 20% to 50% of normal.*<br>• *Azotemia appears, usually associated with anemia and hypertension, Polyuria and nocturia can occur as a result of decreased concentrating ability.*<br>• *Signs and symptoms of renal failure first appear during this stage*<br>• *Sudden stress (e.g. with nephrotoxins) may precipitate uremia.* |
| ***Chronic Renal Failure (CRF)*** | ***Less than 20*** ***(Percent of normal)*** | • *The GFR is less than 20% of normal.*<br>• *The kidneys cannot regulate volume and solute composition*<br>• *Patients develop edema, metabolic acidosis, and hyperkalemia.*<br>• *Overt symptoms of renal failure typically appear during this stage*<br>*Overt uremia may ensue, with neurologic, gastrointestinal, and cardiovascular complications.* |
| ***End-Stage-Renal Disease (ESRD)*** | ***Less than 5*** ***(Percent of normal)*** | • *The GFR is less than 5% of normal;*<br>• *This is the terminal stage of uremia.* |

53. **Answer is C (>60%):** *'Fluid Electrolytes with Clinical Applications' 7th (Cengage Learning) 2004*

***Signs of renal failure become apparent when renal function deteriorates by more than 60% ( residual renal function between 20-50%) while overt symptoms usually develop only after renal function has deteriorated by >75 – 80% (residual renal function <20%)***

54. **Answer is C (70-80%):** *Refer previous question*

***Overt symptoms usually develop only after renal function has deteriorated by >75 – 80% (residual renal function <20%).***

55. **Answer is C (20%):** *Robbins 8th/ 907*
*Renal Failure is defined as Residual Renal Function mass less than 20 percent of normal.*

| Pathological Classification of Chronic Kidney Disease(CKD) | Residual Functional Renal Mass Residual GFR (% of Normal) |
|---|---|
| *Diminished Renal Reserve* | *50 to 80 percent of Normal* |
| *Renal Insufficiency* | *20 to 50 percent of Normal* |
| *Chronic Renal Failure* | *Less than 20 percent of normal* |
| *End-Stage Renal Disease* | *Less than 5 percent of normal* |

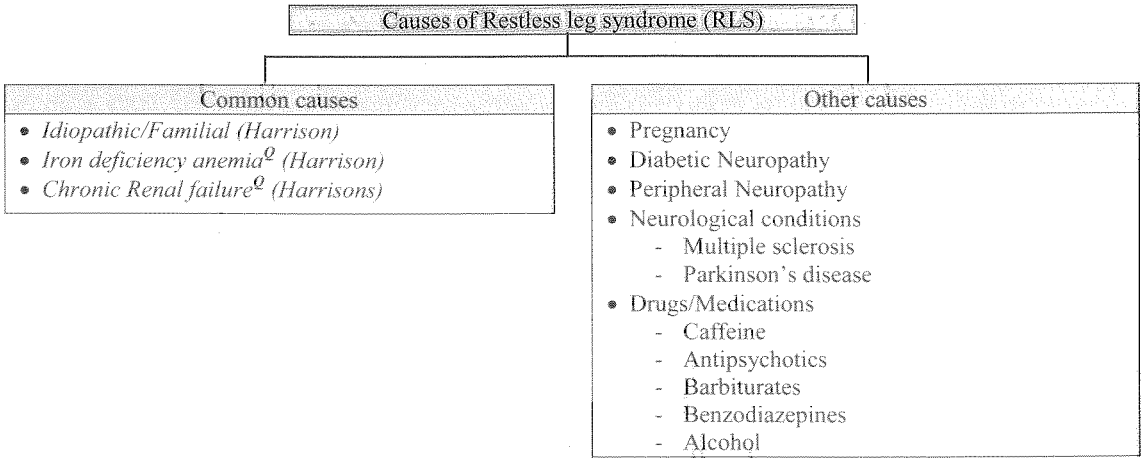
***Q Signs and Symptoms of Renal Failure are evident in the stage of Renal Insufficiency.***

56. **Answer is C (Diabetes Mellitus):** *Harrison 18th/ 2310*

*The most common cause of Chronic Renal Failure in adults is Diabetic Nephropathy (most often secondary to Type-2 Diabetes Mellitus).*

57. **Answer is C (Chronic Renal Failure):** *Harrison 18th/218, 2317; Harrison 17th/176, 1768; The 5 minute Clinical Consult (2007)/1494*

***Iron deficiency and chronic renal failure may cause Restless leg syndrome*** *– Harrison 17th/176*




58. **Answer is B (Hypocalcemia):** *Harrison 15th/ 1555, 16th/1656; 17th / 1764, 1768; Harrison 18th/2317; Adam's 8th / 970*

'The total plasma calcium concentration in CRF patient is significantly low. ***Patient with chronic renal disease*** ***tolerate the hypocalcemia quite well and rarely is a patient symptomatic*** ***from the decreased calcium concentration.*** This may be partly due to concomitant acidosis.' - *Harrison*

*Hyponatremia, acidosis and hyper osmolarity can lead to various CNS manifestation as lethargy, altered mentation, seizure, coma, and paralysis etc.*

59. **Answer is A (Metabolic Acidosis):** *Harrison 17th /1764; Harrison's 18th/2312*

***Chronic Renal Disease / Failure is commonly associated with metabolic acidosis.***

*'Metabolic acidosis is a common disturbance in advanced chronic Renal Disease'- Harrison's 18th/2312*

**60. Answer is A (Hypercalcemia):** *Harrison 18th/ 2311;2312; Conn's Current Therapy 2012/ 885; Wylie Churchill-Davidson's A Practice of Anesthesia 7TH/312*

***Chronic Renal Failure is typically associated with Hypocalcemia.***
*Hypocalcemia, Hyperphosphatemia and subsequently elevated PTH levels lead to renal osteodystrophy.*

| ***Typical Electrolyte Abnormalities in Chronic Renal Failure*** |
|---|
| *Hyponatremia (Hypernatremia may be seen)* |
| *Hypocalcemia* |
| *Hyperkalemia* |
| *Hyperphosphatemia* |
| *Hyperuricemia* |
| *Hypermagnesemia* |

***Hypokalemia** is not common but may be seen and usually reflects markedly reduced dietary potassium intake. Hypokalemia may also occur as a result of primary renal potassium wasting in association with solute transport abnormalities such as Fanconi's anemia, RTA etc.*

**61. Answer is B (Hypophosphatemia):** *Harrison 14th/ 1516; 15th/ 1553 t; 16th/1655; 17th/ 1763 (t. 274.31); Harrison 18th/p 2311 (Table: 280.4)*

*Hypophosphatemia has not been mentioned as a manifestation in Uremia*

**62. Answer is C (Hypercalcemia):** *Harrison 14th/ 1516; 15th/ 1553 t; 16th/1655; 17th/ 1763 (t. 274.31)*

***Chronic Renal Failure is associated with Hypocalcemia and not hypercalcemia.***

**63. Answer is D (Hyperphosphatemia):** *CMDT*

*Serum phosphorus in renal osteodystrophy is either high or normal.*

*The disorders of calcium, phosphorus and bone in chronic renal failure are referred to as Renal Osteodystrophy. In CRF as GFR decreases below 25% of normal, phosphorus excretion is impaired leading to hyperphosphatemia which in turn leads to hypocalcemia, which stimulates secretion of Parathormone, which has a phosphaturic effect and normalizes serum phosphorus.* ***Thus serum phosphorus in renal osteodystrophy is either high or normal.***
***While in Osteomalacia there is hypophosphatemia*** *(CMDT 09/781).*

**64. Answer is A (Post streptococcal GN):** *Robbins 6th/ 951; API / 652, 656; Harrison 16th/1680; Harrison 17th / 1787 Harrison 18th/p 2340*

*Acute post streptococcal GN is a cause of acute Renal failure and not Chronic Renal Failure. The other types of GN listed in the question are causes of CRF.*
***In Post Streptococcal Gn*** *(Acute GN): 95% of the affected children recover. The remaining of who do not recover, develop a Rapidly Progressive form of Glomerulonephritis and land up in ACUTE RENAL FAILURE.*

**65. Answer is B (Increased capillary density at distal half of nails):** *Oxford Textbook of clinical Nephrology 3rd/1883*

*The increase in capillary density of nail bed accounts for the band of discolouration*—*Oxford Text book of Clinical Nephrology*

**Half and Half Nail: Typical nail sign in Uraemia**

- In half-and half nail, two portions can be distinguished separated almost horizontally by a clear line of demarcation.
- Proximally the nail has a dull whitish ground glass appearance Distally the nail bed, is red, pink or brown (occupies 20-60% of total nail length)
- When pressure is applied, the discolouration does not fade completely
- Change can affect single nails or all nails of the hands, feet or both

**Pathology /Histology**

- *The disorder is believed to result from increase in capillary density of the nail bed*
- *The number of capillaries under the nail plate is increased, with remarkable thickening of the capillary walls*
- *The histology of the nail plate itself shows no change and it contains no melanin.*

**66. Answer is D (Azotemia):** *Irwin and Rippe's Intensive Care Medicine (Lippincott Williams & Wilkins, 2008) 6th/ 988; Neurocritical Care (Cambridge University Press) 2009/387; Manual of Extracorporeal Membrane Oxygen in the ICU (JP) 2013/139*

*Azotemia (in the absence of Uremia) is only a relative indication for dialysis.*

*Intractable Fluid Overload, Intractable Hyperkalemia and Uremic Encephalopathy are life threatening manifestations of Renal Failure that require Emergent Dialysis.*

**Traditional Indications for Dialysis**

| *Absolute (Typically Life Threatening)* | *Relative (Typically Non- Life Threatening)* |
|---|---|
| • *Uremic Manifestations*<br>▪ *Uremic Encephalopathy or Neuropathy*<br>▪ *Uremic Serositis (Uremic Pericarditis)*<br>• *Intractable Fluid Overload refractory to diuretics*<br>• *Intractable Hyperkalemia refractory to medical therapy*<br>• *Persistent Metabolic Acidosis refractory to medical therapy* | • *Azotemia in the absence of Uremia*<br>• *Persistent Hypercalcemia, Hypocalcemia, Hyperphosphatemia, Hypermagnesemia or Hyperuricemia refractory to medical therapy*<br>• *Severe and Persistent Nausea and Vomiting*<br>• *Significant Malnutrition and or weight loss*<br>• *Hypertension not responding/poorly responding to medications*<br>• *Bleeding exacerbated by Uremia* |

**67. Answer is B or D (Peripheral Neuropathy or Seizures):** *Harrison 17th/1763 Harrison 18th/p 2310, 3311*

*The response to dialysis in Peripheral Neuropathy and seizures is variable. These abnormalities may persist even after initiation of dialysis.*

**Effect of dialysis and related therapy:**

(I) denotes an abnormality that usually improves after dialysis and related therapy
(P) denotes an abnormality that tends to persist or even progress after dialysis and related therapy
(D) denotes an abnormality that usually develops after dialysis and related therapy

| **Fluid and electrolyte disturbances** | **Neuromuscular disturbances** | **Dermatologic disturbances** |
|---|---|---|
| Volume expansion (I) | Fatigue (I) | Pallor (P) |
| Hyponatremia (I) | Sleep disorders (P) | Hyperpigmentation (I, P or D) |
| Hyperkalemia (I) | Headache (P) | Pruritus (P) |
| Hyperphosphatemia (I) | Impaired mentation (I) | Ecchymoses (I) |
| **Endocrine metabolic disturbances** | Lethargy (I) | Nephrogenic fibrosing dermopathy (D) |
| Secondary hyperparathyroidism (I or P) | Asterixis (I) | Uremic frost (I) |
| Adynamic bone (D) | Muscular irritability | **Gastrointestinal disturbances** |
| Vitamin D deficient osteomalacia (I) | Peripheral neuropathy (I or P) | Anorexia (I) |
| Carbohydrate resistance (I) | Restless leg syndrome (I or P) | Nausea and vomiting (I) |
| Hyperuricemia (I or P) | Myoclonus (I) | Gastroenteritis (I) |
| Hypertriglyceridemia (I or P) | Seizures (I or P) | Peptic ulcer (I or P) |
| Increased Lp(a) level (P) | Coma (I) | Gastrointestinal bleeding (I, P or D) |
| Deacreased high density lipoprotein level (P) | Muscle cramps (P or D) | Idiopathic ascites (D) |
| Proteinenergy malnutrition (I or P) | Dialysis disequilibrium syndrome (D) | Peritonitis (D) |
| Impaired growth and development (P) | Myopathy (P or D) | **Hematologic and immunologic disturbances** |
| Infertility and sexual dysfunction (P) | **Cardiovascular and pulmonary disturbances** | Anemia (I) |
| Amenorrhea (I/P) | Arterial hypertension (I or P) | Lymphocytopenia (P) |
| β2-Microglobulin associated amyloidosis (P or D) | Congestive heart failure or pulmonary edema (I) | Bleeding diathesis (I or D) |
| | Pericarditis (I) | Increased susceptibility to infection (I or P) |
| | Hypertrophic or dilated cardiomyopathy (I, P or D) | Leucopenia (D) |
| | Uremic lung (I) | Thrombocytopenia (D) |
| | Accelerated atherosclerosis (P or D) | |
| | Hypotension and arrhythmias (D) | |
| | Vascular calcification (P or D) | |

68. **Answer is B (Erythropoietin Stimulating Agents):** *Harrison 18th/2316; Revised European Best Practice Guidelines for the Management of Anaemia in Patients with Chronic Renal Failure*
*(Link: http://www.european-renal-best-practice.org/content/ebpg-european-best-practice-guidelines-documents*

***Erythropoiesis-stimulating agents (ESAs) have emerged as the treatment of choice for anemia in chronic renal disease.***
*Erythropoiesis-stimulating agents (ESAs) should be given to all patients with chronic kidney disease (CKD) with haemoglobin levels consistently below 11 g/dl. This applies equally to:*
- *Patients with CKD (stages 1–5) developing anaemia*
- *Patients with CKD stage 5 treated with haemodialysis (HD) or peritoneal dialysis (PD)*
- *Transplant patients with chronic renal insufficiency and anaemia.*

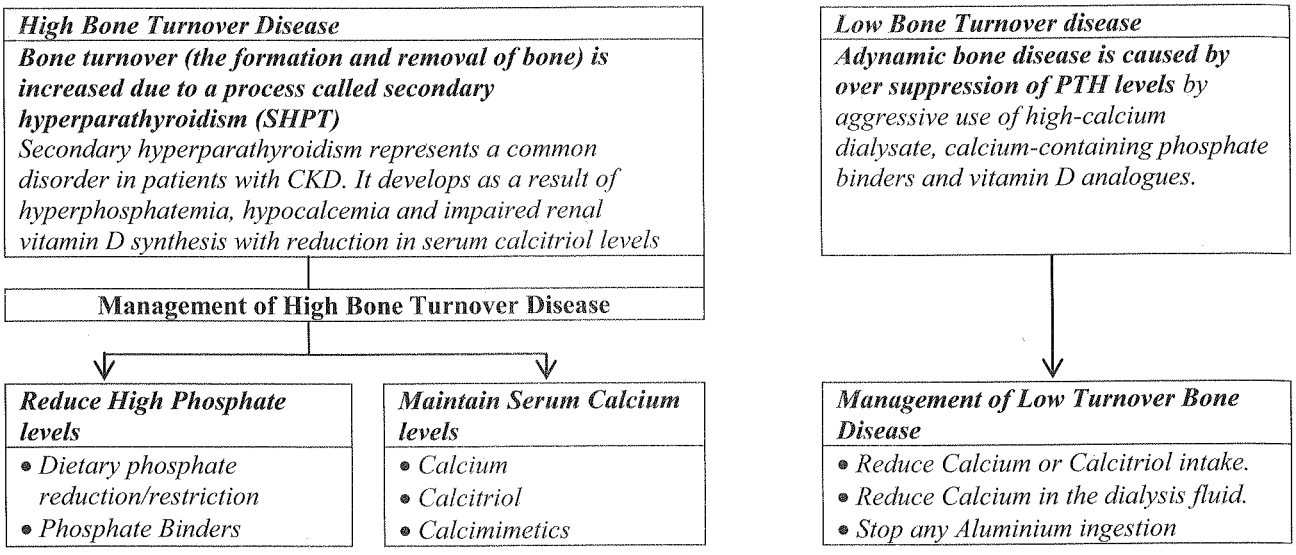
**Strategies for treatment of Anemia in Chronic Renal Failure**

| Erythropoiesis-stimulating agents (ESAs) | Blood Transfusion | Androgens |
|---|---|---|
| • ***Erythropoiesis-stimulating agents (ESAs) have emerged as the treatment of choice for anemia in chronic renal disease.*** | • ***Red blood cell transfusions should be avoided,*** *if at all possible, in patients with chronic kidney disease (CKD), especially those awaiting kidney transplantation.* | • *Prior to the introduction of ESA therapy, androgens were widely used in the treatment of renal anaemia. There is evidence that androgens may potentiate the effect of exogenous erythropoietic protein and also stimulate erythropoiesis by enhancing erythrocyte stemcell differentiation* |
| • *They should be given to all patients with chronic kidney disease (CKD) with haemoglobin (Hb) levels consistently below 11 g/dl [haematocrit (Hct) <33%]* | • *Transfusions should not be given unless patients have one or more of the following: Symptomatic anaemia (fatigue, angina, dyspnoea) and/or associated risk factors (diabetes, heart failure, coronary artery disease, arteriopathy ) Acute worsening of anaemia due to blood loss (haemorrhage or surgery) or haemolysis Severe resistance to, or hyporesponsiveness to ESA therapy, e.g. due to the presence of a haematological disease or severe inflammatory systemic disease.* | • *The risk of liver disease and malignancy, virilisation and hirsutism in women, priapism in men and disfiguring acne in patients of both sexes may outweigh the benefits of androgen therapy in most anaemic patients.* |
| • *All chronic kidney disease (CKD) patients with renal anaemia undergoing treatment with an erythropoiesis-stimulating agent (ESA) should be given supplementary iron to maintain adequate bone marrow iron stores* | | • ***Androgens may be an effective alternative therapy in countries where ESAs are not available*** |
| • *Intravenous administration is the optimum route for the delivery of iron to patients with CKD, as* ***oral iron is poorly absorbed in uremic individuals.*** | | |

69. **Answer is D (Phosphate Binders):** *Harrison 18th/ 3109;*

*The initial treatment of secondary hyperparathyroidism in renal osteodystrophy is management of high phosphate levels by dietary restriction and the use of Phosphate binders.*

*The objectives of management are to maintain blood levels of calcium and phosphorous to as close to normal as possible, to prevent or treat established hyperparathyroidism early and to prevent parathyroid hyperplasia.* ***Phosphate retention begins early in the course of CKD, perhaps as early as in stage 2 and participates in the development of secondary hyperparathyroidism. Central to the management of high-turnover bone disease is controlling the serum phosphate levels. This may be achieved by dietary phosphate restriction or by the use of phosphate binders.***
*Phosphate-binder therapy is recommended when serum phosphate concentrations are elevated despite patient compliance with dietary phosphate restriction. Calcium-based phosphate binders are often recommended as the initial binder therapy.*




**70. Answer is A (Cardiovascular Disease):** *Cecil Medicine: Expert Consult (Elsevier) 2011/ 820*

***The most common cause of death in patients on chronic dialysis is Cardiovascular Disease.***

After cardiovascular disease, infections are the second most common cause of death of patients receiving long-term dialysis.

*Cardiovascular disease is the most common cause of death among patients with chronic kidney disease (ESRD)*
*Cardiovascular disease is the most common cause of death in patients requiring renal replacement therapy (RRT)*
*Cardiovascular disease is the most common cause of death among patients receiving long-term dialysis*
***Infection is the most common cause of death in patients dialyzed for acute renal failure.***

**71. Answer is B (Infection):** *Replacement of Renal Function by Dialysis (Springer) 2004/ 1193 ; Replacement of Renal Function by Dialysis (Springer) 1996/ 828 ; Critical Care Medicine: Principles of Diagnosis and Management in the Adult (Elsevier) 4th/ 979.e3*

***The most common cause of death in patients dialyzed for acute renal failure is Infection.***

*Infections are the most common cause of death in patients dialyzed for Acute Renal Failure. Infection is often complicated by progressive sequential system failure. Cardiovascular disease is the next most common cause of death' - Replacement of Renal Function by Dialysis (Springer).*

**72. Answer is C (Aluminium):** *Chronic Renal Disease (Elsevier) 2014/ 436; Harrison's 18th/ Chapter 281*

***Aluminium is the most common trace element in Dialysis patients associated with risk of Osteomalacia.*** *Studies have also shown that patients on long term dialysis (hemodialysis) who are exposed to dialysate containing high aluminium concentrations are at increased risk of osteomalacia.*

**Aluminium in Patients on Long Term Dialysis:**

| | |
|---|---|
| ***Anemia*** | *Aluminium can compete for key enzymes involved in synthesis of hemoglobin (delta-aminolavelunic acid dehdratase and heme synthetase) resulting in development or worsening of anemia* |
| ***Osteomalacia*** | *Aluminium accumulation and deposition in bone can result in reduced bone mineralization and Osteomalacia. Aluminium induces Osteomalacia in chronic haemodialysis patients by binding to the calcification front, thereby inhibiting mineralization of osteoid. This form of Osteomalacia is vitamin D resistant* |
| ***Encephalopathy*** | *Accumulation of Aluminium in brain tissue can present with memory loss, pseudo-parkinsonian gait, tremor and progress to seizures , dementia and death* |

**73. Answer is A (Reverse Urea Effect):** *Replacement of Renal Function by Dialysis (Springer) 4th/ 422*

*Dialysis disequilibrium is characterized by neurologic symptoms of varying severity that are thought to be due primarily to cerebral oedema presumably caused by the 'reverse urea effect' (The significant urea gradient between blood and brain after dialysis, with, as a result, an inflow of water into the brain causing cerebral edema)*

**Dialysis disequilibrium syndrome** (DDS), refers to the occurrence of neurologic signs and symptoms, attributed to cerebral edema, during or following shortly after initiation of haemodialysis. Cerebral edema and Raised intracranial pressure have been established as central to the diagnosis of DDS. Several mechanisms have been proposed however no consensus exists on the exact mechanism of Dialysis Disequilibrium Syndrome. Reverse urea effect is the most widely accepted underlying mechanism.

*Dialysis disequilibrium syndrome is most commonly attributed to a reverse urea effect*

Urea is cleared more slowly from the brain than from the blood. This creates an osmotic gradient resulting in a net flow of water into the brain leading to (transient) cerebral edema. Symptoms include headache, nausea, emesis, blurred vision, muscular twitching, disorientation, delirium, hypertension, tremors, and seizures. The condition tends to be self-limited and subsides over several hours.

**74. Answer is B (Infusion of insulin and glucose):** *Harrison 18th/p 358, 359; 17th/284; Primer on kidney disease 4th/118*
*'Intravenous insulin is the fastest way to lower serum potassium levels' – Primer on Kidney Diseases 4th/118*

**Management of Hyperkalemia**

**First step**

Stabilize Myocardium

| Method | Onset of action |
|---|---|
| Calcium gluconate or Calcium chloride | 3 to 5 minutes (effect begins within minutes and is marked by Improvement in ECG appearance) |

**Second Step**

Reduce serum $K^+$ levels by shifting $K^+$ from extracellular to intracellular fluid

| Method | Onset of action |
|---|---|
| Insulin (Glucose) | Within 15 minutes *This is the fastest method* |
| Beta agonists (Albuterol) | In about 30 minutes |
| Sodium bicarbonate | At least 3-4 hours |

**Third step**

Remove excess potassium from the body

| Method | Comment |
|---|---|
| Diuretics | Works only if patient has adequate kidney function |
| Resin exchangers (Kayexalate) (sodium polystyrene sulfonate) | • Slow acting (Requires 1-2 hrs before plasma $K^+$ decreases)<br>• Removes $K^+$ from blood into gut in exchange for an equal amount of $Na^+$. |
| Hemodialysis | Definitive treatment of choice in patients with advanced renal failure and severe hyperkalemia |

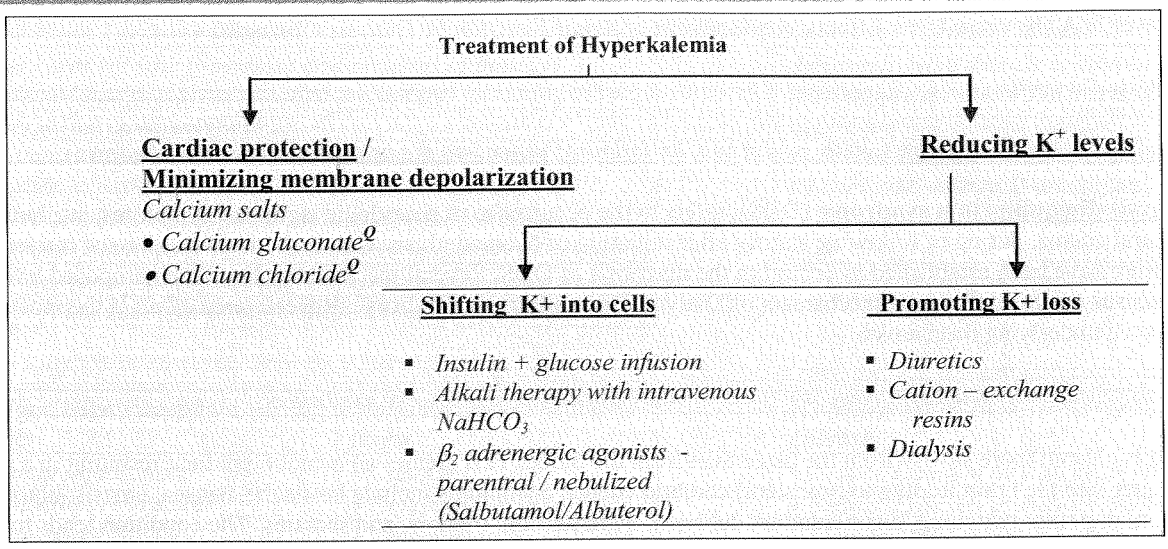
**75. Answer is C and D (Calcium chloride and sodium bicarbonate):** *ALS manual of Resuscitation Council UK 5th*

*Tall Peaked T waves on ECG indicate cardiac toxicity secondary to severe hyperkalemia. Management includes immediate administration of* ***Calcium salts*** *(Calcium gluconate or Calcium chloride) to counteract the myocardial effects of hyperkalemia*
***Sodium bicarbonate*** *helps reduce serum potassium concentration by redistributing potassium and shifting $K^+$ into cells.*

**76. Answer is D (Beta blocker)** : *Harrison 16th / 262-263; 17th / 284; Harrison 18th/p 358, 359 ALS Manual:Resuscitation council UK; 5th edition*

*Beta blockers have no role in management of hyperkalemia*

***Parenteral or Nebulrized Beta 2 agonist*** may be useful by promoting cellular uptake of $K^+$.***Calcium gluconate*** *provides cardiac protection by decreasing membrane excitability, white* ***Insulin and Sodium bicarbonate*** *decrease plasma $K^+$ concentration by shifting $K^+$ into cells.*




**Advanced Life Support Guidelines for Treatment of Hyperkalemia**

| Mild elevation (5.5-6 mmol/L) | Moderate / severe elevation without ECG changes (>6 mmol/l) | Moderate / severe elevation With toxic ECG changes (>6 mmol/l) |
|---|---|---|
| Remove K+ from body<br>▪ Cation exchange resins<br>▪ Diuretics<br>▪ Consider dialysis | Remove K+ from body<br>▪ Dextrose / insulin infusion ( +/-)<br>▪ Nebulized salbutamol<br>▪ Intravenous NaHCO3 (+)<br>▪ strategies as for mild elevation | First stabilize the heart / Antagonize the toxic effects of Hyperkalemia.<br>Calcium gluconate (+)<br>Other strategies |

77. **Answer is C (CMV):** *Bailey & Love's Short Practice of Surgery 25TH/ 1416; Critical Care Nephrology Elsevier Health Sciences) 2008/1667*

***CMV is the most common viral infection after Kidney Transplantation.***

*'CMV is the single most important viral infection in renal transplant recipients'- Critical Care Nephrology*

78. **Answer is D (EBV):** *'Post Transplant Lymphoproliferative Disorders' (Springer) 2010/10: Lippincott Williams & Wilkins, 2010/ Chapter 24*

***The most common virus implicated in Post-Transplant-Lymphoproliferative-Disorder (PTLD) is Epstein Barr Virus (EBV).***

*Post-Transplant Lymphoproliferative Disease (PTLD) is a well-recognized complication of both solid organ transplantation (SOT) and allogeneic hematopoietic stem cell transplantation (HSCT). It is one of the most common post-transplant malignancies. In most cases, PTLD is associated with Epstein-Barr virus (EBV) infection of B cells, either as a consequence of reactivation of the virus post-transplantation or from primary EBV infection. In cases of primary infection, EBV may be acquired from the donor graft or, less commonly, from environmental exposure.*

## Tubulointestinal Disease

79. **Answer is D (Aminoglycosides):** *Harrison 18th/ 2367*

*Aminoglycosides cause acute tubular necrosis and not acute interstitial nephritis.*

***Therapeutic Agents causing Acute Interstitial Nephritis***

| *Antibiotics* | *Analgesics* | *Diuretics* | *Anticonvulsants* | *Miscellaneous* |
|---|---|---|---|---|
| • β-lactams<br>• Sulfonamides<br>• Quinolones<br>• Vancomycin<br>• Erythromycin<br>• Minocycline<br>• Rifampin<br>• Ethambutol<br>• Acyclovir | • NSAIDS<br>• COX-2 inhibitors | • Thiazides,<br>• Loop diuretics<br>• Triamterene | • Phenytoin,<br>• Valproate,<br>• Carbamazepine,<br>• Phenobarbital | • Proton pump inhibitors,<br>• H2 blockers,<br>• Captopril,<br>• Mesalazine,<br>• Indinavir,<br>• Allopurinol |

**80. Answer is B (INH):** *Harrison 18th/p 2367 Harrisons 17th/ 1807 Harrisons 16th/1702*

***INH is not associated with interstitial nephritis***

*Beta Lactom antibiotics, Diuretics and Allopurinol may all be associated with interstitial nephritis*

**81. Answer is A (Interstitial Nephritis):** *Harrison 16th/1703; 17th/1806, 1807; (t-279.2) Harrison 18th/p 2367 Robbin's illustrated 6th/971*

***In interstitial nephritis there occurs damage to distal tubules, which results in impaired sodium reabsorption and hence the so called 'salt wasting'.***

**Tubulointerstitial nephritis-**

*This is a group of renal disease characterized by predominant involvement of the* ***tubules*** *and* ***interstitium*** which leads to defect in the ability of the kidney to concentrate urine.

**<u>These are chracterised by :</u>**

| Defect | Causes(s) |
|---|---|
| **Salt wasting** | **Distal tubular damage with impaired sodium reabsorption** |
| *Reduced glomerular filtration rate* | Obliteration of microvasculature and obstruction of tubules |
| Fanconi syndrome | Damage to proximal tubular reabsorption of glucose, aminoacids, phosphate, and bicarbonate |
| Hyperchloremic acidosis | Reduced ammonia production<br>Inability to acidify the collecting duct fluid (distal renal tubular acidosis)<br>Proximal bicarbonate wasting |
| Tubular or small-molecular weight preoteinuria | Failure of proximal tubule protein reabsorption |
| Polyuria, isothenuria | Damage to medullary tubules and vasculature |
| Hyperkalemia | Potassium secretory defects including aldosterone resistance |

**82. Answer is C (PNH):** *Fundamentals of Uroradiology (1999) /64; 20 common problems in urology (2001)/156 Harrisons 17th*

***PNH is not associated with necrotizing papillitis or papillary necrosis.***

*Diabetes milletus, analgesic abuse (salicylate poisoning) and Renal vein thrombosis are documented causes for renal papillary necrosis.*

**Renal Papillary Necrosis**

- Renal papillary necrosis is typically caused by ischaemic necrosis and sloughing of Renal Papllae (The papillary tip is the apex of renal pyramid)
- It is clinically charachterized by
  - *Loin Pain*
  - *Hematuria*
  - *Variable degree of renal impairment*

**Etiology / Predisposing factors**

- Diabetes and analgesic abuse (NSAIDS) are the most common predisposing factors
- The Acronym POST CARD is traditionally used to enlist the causes of papillary necrosis but it does not put the causes in a useful order of incidence

| | |
|---|---|
| P | Pyelonephritis |
| O | Obstruction |
| S | Sickle –cell disease |
| T | Tuberculosis |
| C | Cirrhosis |
| A | Analgesic abuse/Alcohol |
| R | Renal vein thrombosis |
| D | Diabetes |

POSTCARD -- causes of papillary necrosis

**83. Answer is B (Tuberculous Pyelonephritis):** *Harrison 18th/2367; Harrison 17th/1807, 1825, 1826; Robbins 7th/1000, 1003, 1004, 1011*

***Tuberculosis is the least important/common cause of necrotizing papillitis amongst the options provided.***

**Causes of Renal Papillary Necrosis /Necrotizing Papillitis**

- *Analgesic Abuse Nephropathy (NSAIDs)*
- *Diabetes Mellitus*
- *Sickle cell Disease*
- *Obstruction in association with infection (pyelonepliritis)*
- *Chronic Alcoholism*
- *Vascular Renal Diseases (Renal vein thrombosis)*

*Dibetese Mellitus and Analgesic abuse are the most frequent causes of Renal Papillary Necrosis*

**84. Answer is A (Salicylate poisoning):** *Harrison 15th/ 1625, 1607; 16th/1703; 17th/1807; Robbins 7th /1003, 1004*

***'Salicylate poisoning' or analgesic abuse nephropathy is one of the most common causes of necrotizing papillitis.***

**85. Answer is C (PNH):** *Harrison 17th/ 1807, 1825, 1826; Refer previous question for references*

***All causes other than PNH are known causes of necrotizing papillitis***

**86. Answer is A (Diabetes Mellitus):** *Dorland's Illustrated Medical Dictionary 28th/ 1104*

***'Renal papillary necrosis, an accompaniment of acute pyelonephritis is most often seen in diabetics and is characterised by necrosis of renal papillae of one or both kidneys with sharped demarcation between necrotic and living tissue'*** *– Dorlands*
*Thus while papillary necrosis is a feature of more than one conditions mentioned in the question, it is most commonly seen with diabetes mellitus.*

**87. Answer is A (Alcohol):** *Harrison 17th /1825*

***Chronic Alcoholism is an established cause of Renal Papillary Necrosis.***

## Glomerular Diseases

### Nephrotic Syndrome

**88. Answer is A (RBC cast in urine):** *CMDT 2005/885, 890; Harrison 18th/p 2337 CMDT 2003/891; 2009/794*

***RBC cast in urine is a feature of Nephritic Syndrome and not nephrotic syndrome.***

| **The other 3 points mentioned are 'essentials' in the diagnosis of nephrotic syndrome :** |
|---|
| 1. Proteinuria : excretion > 3.5g/1.73 m2 per 24 hrs. Q |
| 2. Hypoalbunemia : albumin < 3g/dl. Q |
| 3. Peripheral edema. Q |

*Hyperlipidemia Q occurs in 50% of those with early nephrotic syndrome and is much more common in patients who excrete larger amounts of protein per day.*

**89. Answer is D (Fibrinogen):** *Harrison 16th/1684, 1685; 17th / 1789, 1790 Harrison 18th/p 2345*

***Nephrotic syndrome is characteristically associated with increased fibrinogen levels – Hyper fibrinogenemia.***

- ***Nephrotic syndrome is characteristically associated with increased fibrinogen levels – Hyper fibrinogenemia.*** *This is due to increase hepatic synthesis, impaired fibrinolysis, and increased platelet aggregability. It is an important factor responsible for hypercoagulability seen in Nephrotic syndrome.* ***Patient of nephrotic syndrome can develop spontaneous peripheral arterial or venous thrombosis.***
  - Renal vein thrombosis Q
  - Pulmonary embolisms.
- ***Serum albumin*** *is decreased* due to proteinuria Q. Hypoalbumnimia is compounded by increased renal catabolism and inadequate albeit increased hepatic synthesis of albumin.
- ***Transferrin*** loss in urine leads to decreased levels of serum transferrin. This is responsible for *iron resistant microcytic hypochromic anemia.* Q
- ***Ceruloplasmin level****, too are decrease* on account of its loss in urine. Q

**90. Answer is B (Fibrinogen):** *Harrison 16th/1684, 1685; Harrison 17th/ 1789, 1790*

***Nephrotic syndrome is characteristically associated with increased fibrinogen levels – Hyper fibrinogenemia.***

| **Proteins increased in nephrotic syndrome** |
|---|
| 1. Fibrinogen |
| 2. Lipoproteins: due to increased synthesis |

*Most proteins are however decreased in Nephrotic Syndrome.*

| **Proteins decreased** | **Consequence** |
|---|---|
| Albumin | Oedema due to hypoalbunimia Q |
| Transferrin | Fe resistant microcytic anemia Q |
| Cholecalciferol binding protein | Hypocalcemia Q |
| Thyroxine binding globulin | Decreased thyroxin (Hypothyroid state) |

**91. Answer is B (Serum Fibrinogen):** *Harrison 16th/1684, 1685; Harrison 17th/ 1789, 1790 Harrison 18th/p 2345*

***Nephrotic syndrome is characteristically associated with increased fibrinogen levels – Hyper fibrinogenemia.***

| **Proteins increased in nephrotic syndrome** |
|---|
| 1. Fibrinogen |
| 2. Lipoproteins: due to increased synthesis |

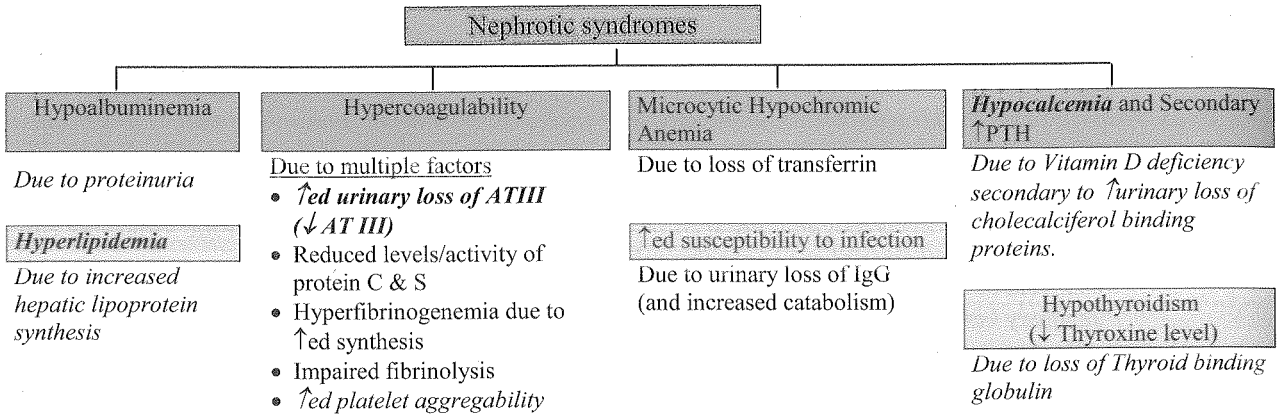
*Most proteins are however decreased in Nephrotic Syndrome.*

| Proteins decreased | Consequence |
|---|---|
| Albumin | Oedema due to hypoalbunimia $^{Q}$ |
| Transferrin | Fe resistant microcytic anemia $^{Q}$ |
| Cholecalciferol binding protein | Hypocalcemia $^{Q}$ |
| Thyroxine binding globulin | Decreased thyroxin (Hypothyroid state) |

**92. Answer is A (Loss of Antithrombin III):** *Harrisons 17th/272*

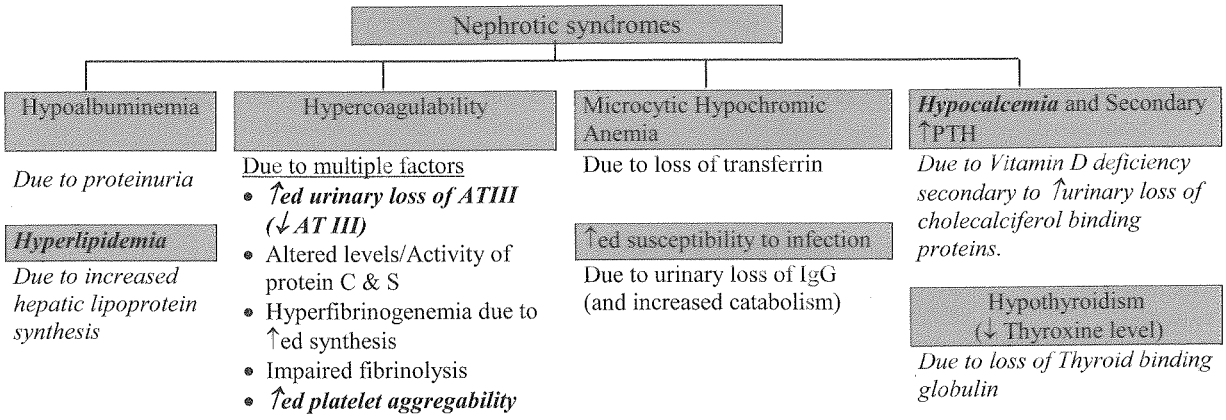
***Loss of Antithrombin III contributes to the hypercoagulable state in Nephrotic syndrome***

*'A hypercoagulable state frequently accompanies severe nephrotic syndrome **due to urinary losses of antithrmbin III**, reduced serum levels of protein C and S, hyperfibrinogenemia and enhanced platelet aggregation' – Harrison 17th/272*




**93. Answer is A and D (Low serum calcium and Platelet activation):** *Harrison 16th/1684; 17th/272 Harrison 18th/p 339*

***Nephrotic syndrome is associated with hypocalcemia and increased platelet activity (↑ed platelet aggregability)***




**94. Answer is E (↓ HDL cholesterol):** *Harrison 16th/1684; Harrison 17th; Clinical Pediatric Nephrology 2nd/173*

***HDL levels are more often decreased in Nephrotic syndrome although they may be normal or elevated but still ↓HDL is the single best answer of choice***

*'The lipid profile in Nephrotic syndrome is characterized by elevations in total plasma cholesterol, very low density lipoproteins (VLDL) and low density lipoproteins (LDL) and often triglycerides levels as well as variable alterations (more often decreased) in high density lipoproteins (HDL)' – Clinical pediatric nephrology 2nd/173*

**Lipid Profile in Nephrotic Syndrome**

**Components that are usually elevated**

- Total cholesterol ↑
- LDL cholesterol ↑

} Increased in majority of patients

- VLDL cholesterol ↑
- Triglycerides ↑

} Increased in patients with severe disease

- Lipoprotein a ($Lp_{(a)}$) ↑ed

**Components that are often normal or reduced**

***HDL cholesterol shows variable alterations however it is more often decreased than elevated.***

- HDL usually normal or Decreased
- HDL may be increased (uncommon)

**95. Answer is A (Diabetes Mellitus):** *CMDT 2007/941; 2009/818; Harrison 16th/1684*

***The most common cause of primary Nephrotic Syndrome in adult is Membranous Nephropathy but this is not provided amongst the options.***

*The most common systemic Renal Diseases associated with Nephrotic Syndrome are Diabetic Mellitus, Amyloidosis and Systemic Lupus Erythematosis (CMDT)*

***As per the prevalence of Diabetes Mellitus is much higher than Amyloidosis, Diabetes Mellitus is the single best answer of choice amongst the options provided.***

**There is no direct reference, quoting Diabetes Mellitus as the most common systemic disease associated with Nephrotic Syndrome. Neverthless, the text from both Harrison and CMDT supports this presumption.**

**Most common causes of Nephrotic Syndrome (Harrison)**

**Systemic Diseases**

- Diabetes Mellitus
- Amyloidosis

***Diabetes Mellitus is more prevalent than Amyloidosis and hence*** *D.M.* ***should be the most common systemic cause of Nephrotic Syndrome***
*Diabetes Nephropathy is the leading cause of End Stage Renal Disease in the U.S.Ω – Harrison*

**Intrinsic Renal Diseases (Idiopathic Nephrotic Syndrome)**

- Membranous Nephropathy
- Minimal change disease
- Focal Glomerulosclerosis
- Membranoproliferative glomerulonephritis

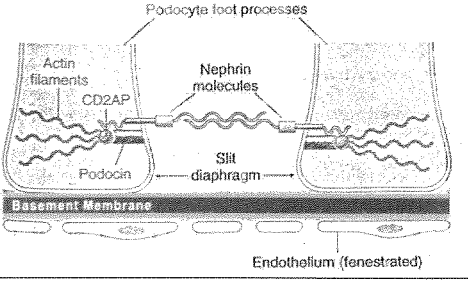
*Membranous Nephropathy is the most common Ω cause of primary Nephrotic Syndrome in adults – CMDT/Harrison*

**96. Answer is C (Nephrin):** *Robbin's 7th/981, 983, 984*

***"A mutation in the Nephrin gene causes a hereditary form of congenital Nephrotic syndrome (Finnish type) with minimal change glomerular morphology"*** *- Robbins 7th/981*

**Nephrin**

- Nephrin is a key component of the slit diaphragm
- It is a zipper like structure between podocyte foot processes that might control glomerular permeability
- The Nephrin gene maps to chromosome 19q13 and is termed as NPHS1.
- ***Several type of Mutations of the NPHS1 gene have been identified and they give rise to congenital nephritic syndrome of the Finnish type.***




**Note:**

- **'Podocin'** has also been recognized as a component of the slit diaphragm
- Podocin is encoded by a gene termed as NPHS 2 and maps to chromosome 1q25-31
  ***Mutation in the podocin gene or NPHS2 lead to an autosomal recessive form of focal segmental glomerulosclerosis***

**97. Answer is B (Hypertrophy of muscle):** *KDT 4th/ 295; KDT 5th/264, 265*

***Atrophy of muscles / muscular weakness is seen.***

| Side effects of corticosteroids: | |
|---|---|
| - *Cushing's habitus* Q | - *Fragile skin, purple striae* Q |
| - ***Hyperglycemia*** Q | - *Muscular weakness* Q |
| - *Susceptibility to infection* | - *Delayed wound healing* Q |
| - *Peptic ulceration* Q | - *Osteoporosis* Q |
| - *Posterior subcapsular cataract* Q | - *Glaucoma* Q |
| - *Growth retardation* | - ***Psychiatric disturbances*** Q |
| - ***Suppression of hypothalamo-pituitary-adrenal axis*** | |

## Nephritic Syndrome and RPGN

**98. Answer is A (Polyuria):** *Harrison 18th/p 2337, 2340 Harrison 17th/1785, 1786; Robbins 7th/973, 974*

***Polyuria is not a feature of acute glomerulonephritis***

**Acute Glomerulonephritis is characterized clinically by the syndrome of acute nephritis or nephritic syndrome.**

| Acute Nephritic Syndrome | |
|---|---|
| *Hypertension* Q | |
| *Hematuria with RBC cast in urine* Q | |
| *Oliguria* Q | |
| *Pyuria* Q | |
| *Azotemia* Q | |
| *Mild to moderate proteinuria* Q<br>*Edema* Q | *Patients with Acute nephritis syndrome also commonly have proteinuria and edema but these are not as severe as those encountered in nephrotic syndrome.* |

**99. Answer is C (Nephritic syndrome):** *Robbins 6th / 935; Robbins 7th*

***Post infective glomerulonephritis are acute glomerulonephritis that usually present with Acute Nephrotic syndrome.***

***It is the classic presentation of Post-Streptococcal or Post-Infective glomerulonephritis.*** *– Robbins 6th/935*

**100. Answer is D (Alports syndrome):** *Robbins 7th/ 977 Harrison 17th/1785 Harrison 18th/p 2338*

***Alports syndrome is not associated with Rapidly Progressive Glomerulonephritis or Crescentric Glomerulonephritis***
*-Harrison 17th /1785*

**Rapidly progressive Glomerulonephritis (RPGN) / Crescentric Glomerulonephritis**

Crescentric Glomerulonephritis is a histopathological diagnosis based upon the presence of 'crescents' in most of the Glomeruli. This type of histopathological picture (crescents) is seen in cases of Rapidly Progressive Glomerulonephritis (RPGN) and hence *RPGN and Crescentric Glomerulo–nephritis are often used synonymously.*

**Causes of Crescenteric Glomerulonephritis (RPGN)**

**Type I RPGN (Anti – GBM Antibody)**

- ***Idiopathic Anti Glomerular Basement membrane disease***
- *Good pasture's Syndrome*

**Type II RPGN (Immune Complex)**

- *Idiopathic*
- ***Acute Post Streptococcal Glomerulonephritis (PSGN)***
- *Lupus Glomerulonephritis (SLE)*
- ***Henoch Schonlein Purpura (HSP)***
- *IgA Nephropathy*
- *Membranoproliferative Glomerulonephritis (Harrisons 17th / 1785)*
- *Cryoglobulinemia (Harrision 17th/ 1785)*
- *Post infectious (After subacute Bacterial Endocarditis) Glomerulonephritis*

**Type III RPGN (Pauci – immune)**

- ANCA – Small Vessel Vasculitis
- *Wegener's granulomatosis*
- *Microscopic polyangitis*
- *Churg – Strauss syndrome*

**Renal disease in Alport's syndrome** (Harrisons 17th /1794)

Patients with Alport's syndrome develop *thinning and splitting of Glomerular basement membrane*[Q], *and chronic glomerulosclerosis*[Q], leading to renal failure. *(Clinically present with hematuria & proteinuria)*
***Rapidly progressive Glomerulonephritis or crescentric glomerulonephritis is not associated with Alport's syndrome.***

**101. Answer is B (Rapidly progressive glomerulonephritis):** *Robbins 6th/ 452; 7th/977; Harrison 16th/1674; 17th / 1785 Harrison 18th/p 2337*

***Rapidly progressive glomerulonephritis also known as Crescentic glomerulonephritis is characterized by the presence of crescents is most of the glomeruli.***

| Crescents are produced by |
|---|
| Proliferation of the *parietal epithelial cells* [Q] of Bowman's capsule |
| Infiltration of *monocytes* [Q] and macrophages. |

**102. Answer is A (Minimal change disease):** *Chandrasoma Taylor, 3rd/ 711; Robbins 7th/977; Harrison 16th/1679; 17th/1786, 1787, 1789 Harrison 18th/p 2337, 2341*

***Minimal change disease is not associated with rapidly progressive glomerulonephritis (RPGN)***

**Rapidly progressive glomerulonephritis** is a syndrome associated with severe glomerular injury.

It does not denote a specific etiologic form of glomerulonephritis.

| *RPGN is defined by 2 criteria.- Chandrasoma Taylor* |
|---|
| Presence of *epithelial crescents* in more than 70% of glomeruli [Q] |
| Occurrence of rapidly progressive renal failure. |

*End stage disease occurs within months.*

**Causes of rapidly progressive glomerulonephritis** *table 48.4 Chandrasoma Taylor 3rd*

| Post infections | Multisystem disease | Drugs | Idiopathic |
|---|---|---|---|
| • *Post-streptococcal Glomerulonephriti* [Q]<br>• *Non streptococcal G.N.*<br>• *Infective endocarditis* [Q] | • *Good pasture's syndrome* [Q]<br>• *SLE* [Q]<br>• *H. S. purpura* [Q]<br>• *Berger's disease* [Q] *(IgA Nephropathy)*<br>• *PAN* [Q]<br>• *Wegener's granulomatosis* [Q]<br>• *Membrano-proliferative glomerulonephritis* | • *Pencillamine* [Q] | • *Type I – with Anti GBM Ab* [Q] *(20 %)*<br>• *Type II-with immune complexes* [Q] *(30 %)*<br>• *Type-III pauci immune (50%)* [Q] |

**103. Answer is C (Diabetic Nephropathy):** *Robbins 7th/977; Harrison 18th/p 2338; 17th/ 1785; Refer previous question*

***Diabetic Nephropathy is not associated with rapidy progressive Glomerulonephritis (RPGN).***

*Acute post streptococcal GN, SLE and Good pasture's syndrome are all associated with Rapidly progressive Glomerulonephritis.*

**104. Answer is C (Microscopic polyangitis):** *Robbins 7th / 977*

***Pauci – immune crescenteric glomerulonephritis (Type III RPGN) is charachteristic of Microscopic Polyangitis***

*Henoch Schonlein Nephritis and Lupus Nephritis are examples of Immune complex mediated crescenteric nephritis (Type II RPGN)*

*Nephritis in Alports syndrome is not associated with crescenteric glomerulonephritis or RPGN*

## Pauci – Immune Crescenteric Glomerulonephritis : Type III RPGN

- Pauci – Immune crescenteric glomerulonephrits represents those cases of RPGN in which glomerular immunoglobulin deposits, either linear or granular are absent
  (Immunoflorescence and electron microscopy in these cases charachteristically show absence of Anti GBM antibodies and immune complexes)
- Most patients with Pauci – immune crescenteric G.N are positive for ANCA (upto 90% of patients), and hence this group is often called ANCA associated RPGN

| Pauci – Immune crescenteric Glomerulonephritis includes |
|---|
| • *Idiopathic RPGN*[Q] |
| • *Wegener's Granulomatosis*[Q] |
| • *Microscopic polyangitis (Microscopic PAN)*[Q] |

**Types of Crescenteric Glomerulonephritis (RPGN)**

| Type I RPGN (Anti – GBM Antibody) | Type II RPGN (Immune Complex) | Type III RPGN (Pauci – immune) |
|---|---|---|
| • **Idiopathic Anti Glomerular Basement membrane disease** | • Idiopathic | *ANCA – Small Vessel Vasculitis* |
| • Good pasture's Syndrome | • **Acute Post Streptococcal Glomerulonephritis (PSGN)** | • Wegener's granulomatosis |
| | • Lupus Glomerulonephritis (SLE) | • Microscopic polyangitis |
| | • **Henoch Schonlein Purpura (HSP)** | • Churg – Strauss syndrome |
| | • IgA Nephropathy | |
| | • Membranoproliferative Glomerulonephritis (Harrisons 17th / 1785) | |
| | • Cryoglobulinemia (Harrision 17th/ 1785) | |
| | • Post infectious (After subacute Bacterial Endocarditis) Glomerulonephritis | |

**105. Answer is A (Rapid recovery) :** *Harrison 14th / 1536 ; 15th / 1581; 16th/1679; API 8th / 747; CMDT 2008/803; Causes of RPGN*

***RPGN is characterised by rapidly progressive renal disease which culminates in End stage renal disease (ESRF) within months after onset. Recovery is rare.***

| RPGN is characterized by a Subacute glomerular inflammation with : |
|---|
| • *Nephritic urinary sediment, i.e. RBC casts, WBC casts* |
| • *Sub-**nephrotic non-selective proteinuria*** (proteinuria < 3.5 g/24 hr) *(selective proteinuria is a feature of minimal change disease)* |
| • *Oliguria and Edema* |
| • *Hypertension* |
| • *Presence **of crescents** pathologically* |

**106. Answer is A (Number of crescents):** *Robbins 6th /453*

***The prognosis of crescentric glomerulonephritis relates to the number of crescents***

*'Prognosis can be roughly related to the number of crescents'* - Robbins

**107. Answer is B (Mesangiocapillary Glomerulonephritis) :** *Harrison 18th/p 2334; Chandrasoma Taylor 3rd /708*

***Mesangiocapillary Glomerulonephritis is the other name for Membranoproliferative glomerulonephritis. It is a type of proliferative Glomerulonephritis.*** *(Harrisons 17th /1789)*

**Proliferative changes in Glomerulonephritis** *(Refer: Chandrsoma Taylor 3rd /702, 708)*

- *Glomerulus contains Endothelial cells, Epethelial cells, and Mesangial cells. Any of the three cell types may undergo proliferation in different types of Proliferativ Glomerulonephritis.*
- *Proliferative changes are not limited to Membranoproliferative and Mesangioproliferative Glomerulonephritis, but may be seen in several other forms of Glomerulonephritis*

**Glomerulonephritis and Proliferative changes**

**Glomerulonephritis without proliferative changes**

| *Glomerulonephritis* | *Proliferative changes* |
|---|---|
| *Minimal change Disease* | *- (Absent)* |
| **Membranous Glomerulonephritis** | *- (Absent)* |
| *Diabetic Nephropathy* | *- (Absent)* |
| **Amyloidosis** | *- (Absent)* |
| **Focal segmental Glomerulosclerosis** | ± Variants with proliferative lesions have been described including cellular lesions with endocapillary hypercellularity- (Harrisons) |

**Glomerulonephritis with proliferative changes**

| *Glomerulonephritis* | *Proliferative changes* |
|---|---|
| *Post streptococcal GN* | *+ (Crescents)* |
| *Antibasement membrane disease (Good – pasture's syndrome)* | *+ (Crescents)* |
| *IgA Nephropathy (Berger's)* | *+ (Mesangial)* |
| *Henoch Schonlein Purpura* | *+ (Mesangial)* |
| *Mesangioproliferative GN* | *+ (Mesangial)* |
| *Membranoproliferative GN* **(Mesangiocapillary GN)** | *+ (Endothelial & Mesangial)* |
| *Focal Glomerulonephritis* | *+ (Focal)* |
| *Secondary Glomerulonephritis SLE / PAN* | *+ Variable* |

Note : Crescents represent proliferation of epethelial cells

**108. Answer is C >B (Membranoproliferative Glomerulonephritis > Cryoglobulinemia):** *Harrison 16th / 1682. 2012; CMDT 2006 / 925*

*The association of generalized edema, hypertension, proteinuria, hematuria along with hypocomplimentemia and positive anti-hepatitis C antibodies may be seen in both Membranoproliferative Glomerulonephritis and Mixed Cryoglobulinemia.*

***With the limited information provided in question MPGN appears to be a better option in comparison to Essential Mixed Cryoglobulinemia for the following reasons:***

- *Cryoglobulinemic Glomerulopathy is most common with the Mixed Cryoglobuliinemias Type II and III that are most common in females and begin in the sixth decade. – Harrison 16tth / 1682*
  ***The patient in question is a male in the 4th decade of life (30years)***
- *Most patients with cryoglobulinemia present with variable combination of stress ulceration, arthralgia, fatigue and Raynaud's phenomenon other than renal manifestations. The fundamental finding is presence of circulating cryoprecipitates.*
  ***The patient in question is not presenting with any of the above features to favour Mixed Cryoglobulinemia over MPGN.***
- ***Membranoproliferative glomerulonephritis is responsible for 80% of all Renal lesions in Essential Mixed Cryoglobunemia.*** *-Harrison 16th / 2012*

**Hepatitis C infection and Glomerular lesions (CMDT 924)**

**Three clinicopathologic glomerular syndromes associated with hepatitis C are**:

- ***Secondary MPGN***
- ***Cryoglobulinemic Glomerulopathy***
- *Membranous nephropathy*

***MPGN is the most common lesion****. These patients typically have haematuria, hypertension, proteinuria and anemia. Hypocomplementemia is very common with C4 typically more reduced than C3.*

**Low complement level nephritis syndromes**

***(Immune complex glonerulonephritis)***

- *Idiopathic proliferative glomerulonephritis*
- *Crescentric glomenelonephritis*
- ***Membranoproliferative glomerulonephritis***
- *Lupus nephritis*
- ***Cryoglobulinemia***
- *Bacterial endocarditis*
- *Shunt nephritis*
- *Post infectious glomerulonephritis (post streptococcal)*

**109. Answer is B > C (Essential mixed cryoglobulinemia):** *Refer Previous question*

***The presence of skin ulceration on clinical examination in a female patient around the 6th decade favors a diagnosis of Essential Mixed Cryoglobulinemia over MPGN.***
*Nevertheless if Essential Mixed Cryoglobulinemia were not amongst the options MPGN would be the single best answer of choice.* ***Membranoproliferative glomerulonephritis is a responsible for 80% of all renal lesions in essential mixed cryoglobulinemia.***

**110. Answer is D (Absence of associated proteinuria is pathognomic) :** *Robbins 6th/962; Robbins 7th/988; Harrison's 15th/1589; Harrison 16th/1690; Harrison 17th / 1788, 1789, Harrison 18th/p 2342, 2343 Chandrasoma Taylor 3rd/7110*

*"Proteinuria may or may not be associated" - above references*

**Berger's Disease/IgA Nephropathy**

| Aetiopathogenesis |
|---|
| *Respiratory or gastrointestinal exposure to environmental agents (viruses, bacteria etc.)* ↓ Genetic or acquired abnormality of immune regulation resulting in *increased mucosal IgA synthesis*[Q] ↓ Formation of circulating *IgA immune complexes*[Q] which are entrapped *in mesangium.*[Q] |

| Microscopic Pathology[Q] | Immunofluorescence | Electron Microscope |
|---|---|---|
| ***Mesangioproliferative** (diffuse) glomerulonephritis > **Segmental** proliferation confined to some glomeruli (**focal** proliferative glomerulonephritis)> Overt crescentric glomerulonephritis (rare)* | *Mesangial deposition of IgA often with C3 and properidin*[Q] *(IgG is present in 50% of cases.)*[Q] | *Electron dense deposits in mesangium*[Q], mesangial hypercellularity, sclerosis |

**Clinical**

***Haematuria :*** Most common presentation is with ***gross haematuria*** *24 to 48 hrs after a pharyngeal / gastrointestinal infection*[Q] / vaccination or strenuous exercise.
***Microscopic haematuria***[Q] detected during routine physical examination may be the presentation.
***Proteinuria*** (Nephrotic syndrome) : *may or may not be present*[Q] *- Robbins*
***Hypertension*** (20-30%) is *unusual at presentation.*[Q]

**111. Answer is B (Mesangioproliferative glomerulonephritis):** *Harrison 18th/p 2342, 2343 Chandrasoma Taylor 3rd/711;*

*IgA Nephropathy is a type of mesangioproliferative glomerulonephritis with IgA deposition in the mesangium*

**Mesangioproliferative Glomerulonephritis:**

| Causes | Typical pathological findings | Typical clinical presentation |
|---|---|---|
| IgA Nephropathy<br>Henoch Schonlein Purpura | Proliferation of mesangial cells and deposition of IgA in matrix | Haematuria<br>Proteinuria<br>Hypertension |

**112. Answer is A (Henoch schonlein purpura) :** *Harrison 18th/p 2342, 2343 Harrison 17th/1788, 1789;Robbins 6th / 965; 7th/990; Chandrasoma Taylor 3rd /712*

***Renal manifestations in henoch schonlein purpura are very similar to those in IgA nephropathy.*** *IgA is deposited in the glomerular mesangium in a distribution similar to IgA nephropathy.*

**Renal manifestations of Henoch Schonlein Purpura include:**

Haematuria (gross or microscopic), proteinuria, and nephrotic syndrome.
Rapidly progressive G.N. may be seen.
*The difficulty in isolating cases of Henoch schonlein purpura from those of Ig A nephropathy has led to the notion that these are spectra of the same disease.*

**113. Answer is A (IgA Nephropathy) :** *Nelsons 18th/2169, 2170-2173; Rudolph Pediatrics 21st /1682*

*Recurrent episodes of painless gross haematuria represent the classic clinical presentation of IgA nephropathy.*
*- Rudolph's Pediatrics 21st/1682*

***Recurrent episodes of gross haematuria***

*Recurrent Gross Haematuria should be distinguished from isolated episodes of gross hematuria, as it is a charachteristic feature of some specific disorders*

| Charachteristic Causes of Recurrent Gross Haematuria (Nelson 18th/2169) | |
|---|---|
| 1. *IgA Nephropathy*<br>2. *Alports syndrome*<br>3. *Thin Glomerular basement membrane disease*<br>4. *Hypercalciuria*<br>5. *Urolithiasis* | *Isolated Glomerular diseases with recurrent Gross haematuria* |

*Recurrent Gross Haematuria must be distinguished from Urethrorrhagea.*
*Urethrorrhagia refers to urethral bleeding in the absence of urine.It is associated with dysuria and blood spots on underwear after voiding .It often occurs in prepubertal boys at intervals, several months apart over a period of many years, and has a benign self limiting cause.*

- ***Recurrent episodes of gross hematuria is a charachteristic feature of IgA Nephropathy***

  *IgA nephropathy is the most frequent glomerular disease in the world (Rudolph)*
  *It presents most commonly in children (patient in question is 6 year old) and young adults.*

  *Recurrent episodes of painless gross (macroscopic) haematuria is the classical presentation of IgA Nephropathy.*

  *Patients classically present with gross haematuria within 1 – 2 days after the onset of an upper respiratory tra infection that typically resolves within 5 days*

  ***IgA Nephropathy is the single best answer amongst the options provided***

- ***Gross Haematuria is an uncommon presentation in Wilm's tumor*** *(CPDT 18th/905)*

  *Wilm's tumor is unlikely to present with recurrent gross haematuria.*

- ***Gross Haematuria is not a feature of Neuroblastoma***

- ***Henoch Schonlein Purpura*** *may present with Gross haematuria in 20 –30% of cases, Gross haematuria however is not as common in H.S. Purpura as in IgA nephropathy and H.S purpura is not listed in the list of suggested diagnosis in a child presently with recurrent Gross Haematuria*

**114. Answer is D (Repeated Gross Hematuria):** *Rudolph Paediatrics 21st/ 1682; Refer IgA Table*

***The most common presentation of IgA Nephropathy is with recurrent episodes of Gross (Macroscopic) Hematuria during or immediately following an upper respiratory tract infection***
*'Recurrent attacks of Painless Gross Hematuria represent the classic clinical presentation of IgA Nephropathy' – Rudolph's Paediatrics*

**115. Answer is A (IgA Raised):** *Current Rheumatology Diagnosis & Treatment 2nd/319, Robbins 7th/990; Chandrsoma Taylor 3rd/712*

***The most common systemic vasculitis in children is Henoch Schonlein Purpura, and the most common primary glomerular disease is IgA Nephropathy. H.S purpura and IgA nephropathy may actually represent spectra of same disease and both are associated with elevated levels of IgA which is the single best answer of choice.***

*Antinuclear Antibodies (ANA) and Antineutrophilic Cytoplasmic Antibodies (ANCA) are characteristicaly Negative and serum complement levels are typically normal.*

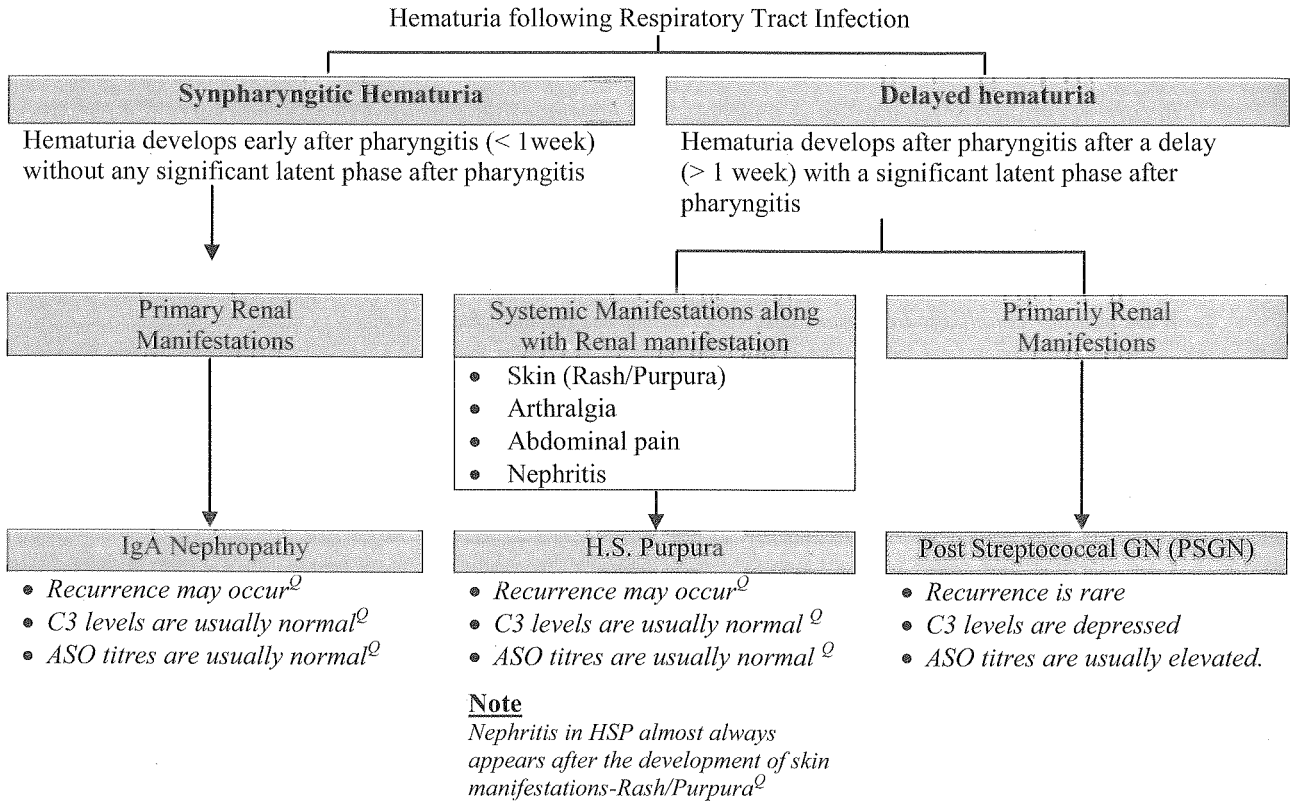
| Laboratory Feature of Renal vasculitis in children due to HSP | |
|---|---|
| • *Serum IgA levels* | *Elevated (60% of patients have an elevated serum IgA)* |
| • *Antinuclear Antibody (ANA)* | *Negative* |
| • *Antineutrophil cytoplasmic Antibodies (ANCA)* | *Negative* |
| • *Complement (C3, C4)* | *Normal*<br>*Even though immune complexes containing IgA are essential to the pathophysiology of HSP, serum complement levels are usually normal* |
| • *Cryoglobulins* | *Negative* |

**116. Answer is A (Increased IgA levels):** *Current Rheumatology Diagnosis and Treatment 2nd/319, Robbins 7th/990; Chandrasoma 3rd/712*

***The most common systemic vasculitis in children is Henoch Schonlein Purpura, and the most common primary of glomerular disease is IgA Nephropathy. H.S purpura and IgA nephropathy may actually represent spectra of same disease and both are associated with elevated levels of IgA which is the single best answer of choice.***

**117. Answer is B (IgA Nephropathy):** *CMDT 2007/939; 2009/813-14; Harrisons 17th/1788; 16th/1690; Harrison 18th/p 2342, 2343 Refer Previous question.*

***Presence of syntharyngitic hematuria (No significant latent phase between hematuria and pharyngitis) suggests a diagnosis of IgA Nephropathy***




**Note**
*Nephritis in HSP almost always appears after the development of skin manifestations-Rash/Purpura*

**118. Answer is B (IgA Nephropathy):** *Harrison 18th/p 2342, 2343; 17th/1789, 1788; 16th/1690, Nelsons 17th/1737, 1738.*

*Recurrent Gross hematuria is a charachteristic feature of IgA Nephropathy A diagnosis of IgA Nephropathy is further supported by the presence of normal complement C3 levels.*

| IgA Nephropathy | Post streptococcal Glomerulonephritis |
|---|---|
| • **Synpharygitic Hematuria**<br>*Hematuria develops usually within 2-4 days of Pharyngitis /URTI*<br>*This is called synpharygitis hematuria since there is no significant latent period between development of hematuria and pharyngitis* | • Delayed Haematuria<br>Hematuria develops 1-3 weeks after pharyngitis /URTI<br>*This is called delayed Hematuria since there s a significant latent period between development of hematuria and pharyngitis* |
| • **Recurrence is common**<br>*'Hematuria occuring in IgA nephropathy typically lasts for several days and then subsides, only to return every few months'*<br>Recurrent Gross Hematuria | • Recurrence is rare<br>*'Complete Recovery occurs in more than 95% of patients with PSGN. One attack confers life long immunity and recurrences are extremely rare* |
| • **Serum complement C3 levels are Normal**<br>C3 levels Normal | • **Serum levels of complement C3 are reduced**<br>C3 levels depressed in > 90% |
| • **Antistreptolysin O titres are usually normal** | • **Antistreptotysin O titres are usually elevated**<br>*'Increased ASO titres are associated with Acute PSGN rather than IgA Nephropathy'* |

**119. Answer is C (IgA Nephropathy):** *Harrison 17th / 1786, 1788; Harrison 18th/p2340, 2342 Nelson 17th / 1737, 1738*

***While, IgA Nephrapathy presents within three days, presentation of poststreptococcal GN is usually delayed to more than 10 days'. As the patient here presents within 3 days diagnosis is IgA nephropathy.***

**Read the following two text facts very carefully**

***IgA Nephropathy:*** The disease affects children and young adults. Patients with IgA nephropathy typically present with gross haematura, often 24 to 48 hrs. after a Pharyngeal or gastrointestinal infection, vaccination or strenous exercise. – *Harrison 16th/1690*

***Poststreptococcal GN :*** Most commonly encountered in children 2 to 6 years old. Glomerulonephritis develops on average 10 days after pharangitis and two weeks after a skin infection with a nephritogenic strain of gp. A Haemolytic streptococci. Those with overt disease present with gross haematuria (red or smokes urine) headache and generalise symptoms such as anorexia, nausea, vomiting, malaise. – *Harrison 16th/1680*

***The crux of it is*** :

- Both are common in children
- Both may present after upper respiratory tract infection.
- Both present with gross haematuria,

***'But while, IgA Nephropathy presents within three days, presentation of poststraptococcal GLN is usually delayed to more than 10 days'.***

**120. Answer is D (Post streptococcal glomerulonephritis):** *Harrison 15th/ 1589; Harrison 16th/1680, 1690; 17th / 1786 Harrison 18th/p 2340, 2342*

*While, IgA Nephropathy presents within three days, presentation of poststreptococcal GN is usually delayed to more than 10 days'.*

| Heamaturia after 10-14 days of URTI | Heamaturia within 3 day of URTI |
|---|---|
| Post streptococcal GN ♀ | IgA nephropathy ♀ |

**121. Answer is C (Glomerulonephritis secondary to skin infection is more common in Summer):** *Harrison 15th/ 1582; Nelson 15th/ 1487; Harrison 17th/*

*'During cold weather post streptococcal glomerulonephritis commonly follows streptococcal pharyngitis; whereas during warm weather, the G.N. generally follows streptococcal skin infection or pyoderma'. - Nelson 15th/1487*

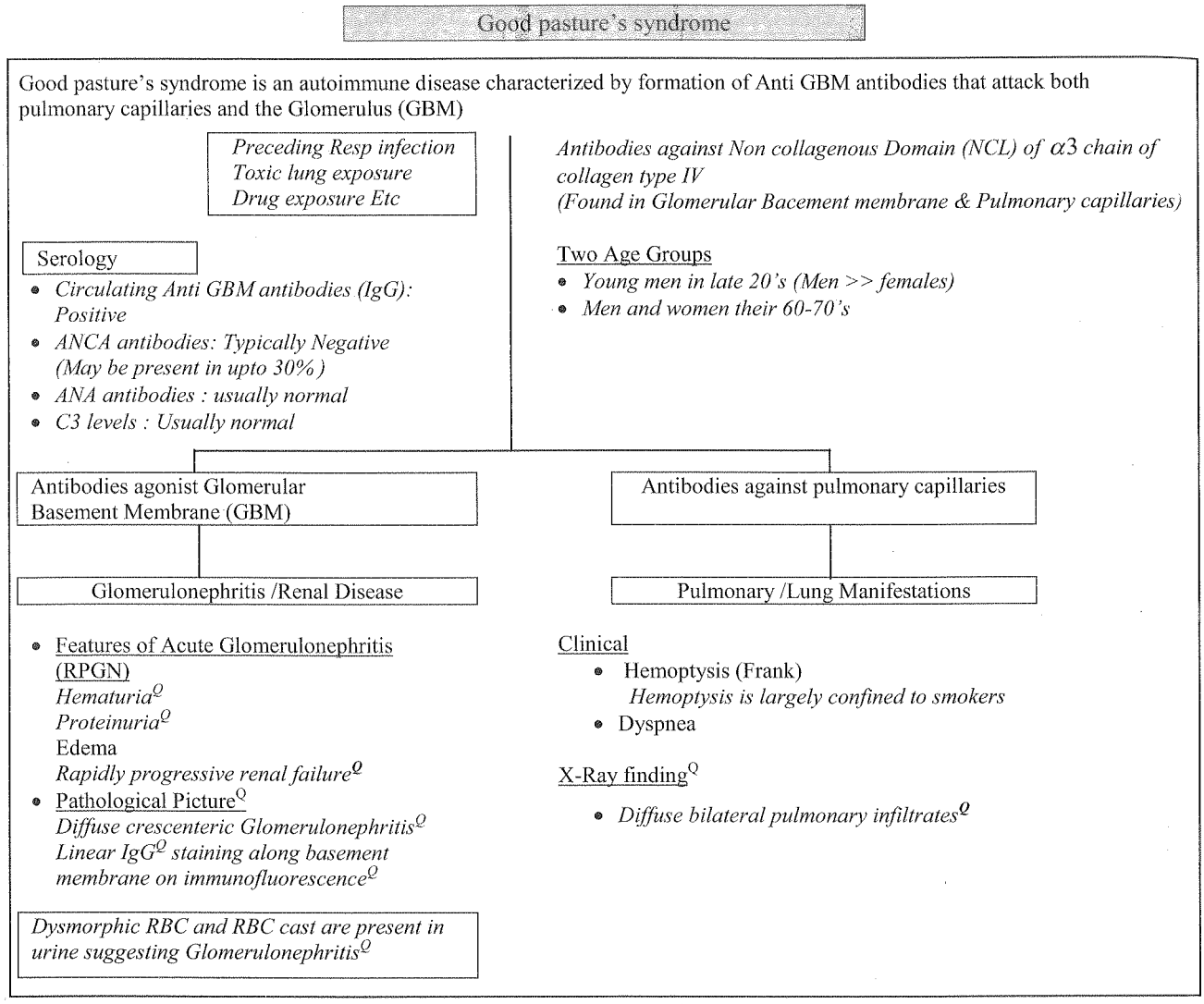
- *"Early systemicantibiotic therapy of Streptococcal throat and skin infection will NOT eliminate the risk of glomerulonephritis". Nelson 15th / 1488*
- *"Recurrence are extremely rare"* Nelson 15th / 1488 .....Immunity to strains causing G.N. is type-specific and long-lasting, and hence repeated infection and nephritis are rare.
- Post streptococcal glomerulonephritis may follow either pharyngitis or, skin infection (pyoderma) with a nephritogenic strain of *group A beta haemolytic streptococci.*
- I could not however, find what percentage of PSGN cases follow pharyngitis and what percentage follow skin infections. [*I looked in Harrison, Robbins, Nelson, CMDT, Ananth Narayan as well as Chandrasoma Taylor*]. All I could gather was that these incidences are relative, depending upon the climatic conditions of the area concerned such that in the tropics, skin infection is more important than pharyngitis as a cause.

  ***The epidemic forms,*** *on the other hand,* ***are seen in children of 2-6 years of age, and are secondary to pharyngitis.*** Thus no exact demarcation in terms of percentages can be made.

## Goodpasture's Syndrome

**122. Answer is A (Goodpasture's syndrome):** *Refer text below; Current Diagnosis and Treatment in Pulmonary Medicine 1st (2003)/211*

*Association of hematuria and hemoptysis suggest a diagnosis of Goodpasture's syndrome.*




**Goodpasture's syndrome and ANCA**

*ANCA is typically negative in Goodpastures syndrome and it is classified as an ANCA negative vasculitis*
*Nevertheless*
*ANCA seropositivity may occur in upto 30 percent of patients with Goodpasture's syndrome.These patients with ANCA have subtle signs of a systemic vasculitis and represent an overlap between goodpastures and either Wegener's granulomatosis (WG) or Microscopic polyangitis(MPA)-Current Diagnosis and Treatment in Pulmonary Medicine 1st (2003)/211*

**123. Answer is A (Good pasture's syndrome):** *Current critical case diagnosis & Treatment 3rd*

*Association of hematuria and hemoptysis suggests a diagnosis of Goodpasture's syndrome*

*Good pasture's syndrome is an autimmune disease charachterized by formation of Anti GBM antibodies, that attack both the pulmonary capillaries (hemoptysis) and the glomerulus (hematuria).*
*The classical presentation is that of a young male smoker with signs of acute glomerulonephritis (hematuria, proteinuria & RBC cast) and hemoptysis associated with bilateral pulmonary infiltrates.*

**124. Answer is B (Goodpasture's Syndrome):** *Refer Goodpasture's Syndrome Table*

*Goodpasture's Syndrome is an autoimmune disease characterized by formation of Anti-Glomerular Basement Membrane Antibodies (Anti-GBM Antibodies) that attack both, Pulmonary Capillaries (Hemoptysis) and the Glomerulus (Hematuria)*
***The association of Hemoptysis and Hematuria along with anti-basement membrane antibodies suggests a diagnosis of Goodpasture's Syndrome***

**125. Answer is D (All of the above):** *Kelly's textbook of Internal Medicine 2nd/694; Harrison 18th/p 2351 Harrison's 17th/1788; Robbins 7th/745, 746; Current Diagnosis &Treatment in Pulmonary Medicine (2003)/211*

*Good pasture's syndrome is typically associated with anti-GBM antibodies, crescenteric glomerulonephritis (RPGN) and diffuse alveolar haemorrhage*

*'Good pasture's syndrome is charachterized by the combination of **Diffuse Alveolar Haemorrhage (DAH)** and **glomerulonephritis (Crescents; RPGN)** associated with **anti-gomerular basement membrane (GBM)antibodies** in serum or evident on immunofluorescent staining of renal or lung tissue. The sine-qua-non of Good pasture's syndrome is the demonstration of linear deposition of Ig -G – immunoglobulin (IgG) along the alveolar capillary or GBM.' - Kelly Essentials of Internal Medicine 2nd/694*

**126. Answer is B (Leucocytoclastic Vasculitis) :** *Refer previous question*

*Leucocytoclastic vasculitis is not a typical feature of Good pasture's syndrome*

Triad of Goodpasture's syndrome (*Ferri's Color Atlas & Text of Clinical Medicine*)

- *Glomerulonephritis$^{Q}$ (RPGN; crescents)*
- *Pulmonary Haemorrhage$^{Q}$ (Diffuse Alveolar Haemorrhage)*
- *Antibodies to basement membrane antigens$^{Q}$ (Anti-GBM antibodies)*

## Alport's Syndrome

**127. Answer is B (Alport's syndrome):** *Harrison 18th/p 2351, 3213 Harrisons 17th/2469, Davidsons 20th /504, Clinical Pediatric Nephrology 2nd/195,196,197,198*

*Alport's syndrome is an inherited disorder characterized by hereditary nephritis, sensorineural deafness and ocular abnormalities particularly lenticonus.*

Clinical Manifestation of Alport's Syndrome (Triad)

*Because it is inherited as an Xlinked disorder, women are usually less severely affected than men.*

Most common inheritance: X Linked (Recessive)
Most common defect : Alpha 5 chain of collagen IV

| Nephritus | Sensorineural Deafness | Ocular Abnormalities |
|---|---|---|
| • Hematuria is the classic presenting feature and occurs early in life | • Sensorineural deafness is the most common extrarenal manifestation in Alport's syndrome | • Anterior Lenticonus is charachteristic (often bilateral) |
| • Proteinuria often develops but its development is usually noticed years after hematuria is first observed (delayed) | • Primarily in the high tone range<br>• Frequently detectable only by an audiogram<br>• Usually not progressive (Harrison) | • Recurrent corneal erosisns and lens opacities are often associated |
| • Chronic Renal Failure develops in most individuals and is often observed in late teens or early 20's | *According to Clinical Pediatric Nephrlogy, hearing loss is progressive* | *Lenticonus together with hematuria is considered pathognomic of classic AS* |

**128. Answer is C (Alport's syndrome):** *Harrison 18th/p 2351, 3213 Harrison's 17th/1794, 2469, Differential Diagnosis in Internal Medicine: From Symptom to Diagnosis by Siegenthaler (Thieme) 2007/877*

***Association of Renal failure with Lenticonus / Keratoconus with a positive family history suggests a diagnosis of Alport's syndrome.***

**Alport's Syndrome**

| Nephrosis / Kidney | Otological (Ears) Symptoms | Ocular (Eye) |
|---|---|---|
| • *Hematuria (Micro /Macro)*<br>• *Proteinuria*<br>• *Progressive **Renal Failure*** | • *Sensorineural hearing loss* (Labyrinthine hearing loss particularly in high frequency) | • ***Lenticonus*** is characteristic<br>• *Cataract (lens opacity)*<br>• *Corneal erosions*<br>• *Keratoconus*<br>*Myopia induced by Lenticonus & keratoconus* |

**129. Answer is A (Alport's syndrome):** *Harrison 18th/p 3213 Davidsons 20th/503, 504, Harrisons 17th/2469 Clinical Pediatric Nephrology 2nd/195, 196, 197, 198*

***Most cases of Alport's syndrome arise from a mutation or deletion of the COL4/A5 gene located on the X chromosome which codes for alpha 5 chain of type IV collagen*** *- Davidson*

## Alport's syndrome

Alport's syndrome is an inherited disorder charachterized by hereditary nephritis, senserineural deafness and ocular abnormalities.
*Alport's syndrome is the most common hereditary nephritis*[Q]

### Genetic defect, Pathology

- Primary pathology in Alport's syndrome is an abnormality in type IV collagen
  (Type IV collagen is the predominant collagen in basement membrane)

| Type IV collagen consists of six different $\alpha$ chains $\alpha 1(IV)$ to $\alpha 6(IV)$ $\alpha 4(IV)$ | | | |
|---|---|---|---|
| α1and α2 : Located on chromosome 13 | : | Genes COLA4A1, COLA4A2 | α3, α4 and α5 chain form a callogen network present in<br>• Glomerular Basement membrane (GBM)<br>• Cochlea<br>• Lens capsule |
| α3 and α4: Located on chromosome 2 | : | Genes COLA4A3, COLA4A2 | |
| α5 and α6 : Located on X chromosome | : | Genes COLA4A5, COLA4A6 | |

- ***The most common form of Alport's syndrome is due to mutation of the COLA4A5 ($\alpha$ – 5 Chain) gene located on the X chromosome***[Q]***.***
- The most common inheritance pattern for Alport's syndrome is X Linked – *Classic Alport's syndrome*

> *Alport's syndrome may be inherited as X-Linked, Autosomal recessive, or Autosomal dominant disorder but classic Alport's syndrome in inherited as an X linked disorder.*

### Clinical Triad

- *Nephritis (Hematuria, Proteinuria, Progressive renal insufficiency)*
- *Sensorineural deafness*
- *Ocular abnormalities (Lenticonus > Recurrent corneal erosisons, corneal opacipies)*

### Pathological Findings in kidney

- *Irregular thickening and thinning of Basement membrane*
- *GBM may appear normal or diffusely thin*
- *Splitting of Lamina and micro granulation's may be seen*

### Treatment and Prognosis

*No specific treatment to slow the progress of this condition.*
*Patients are good candidates for Renal transplantation.*
*Recurrence of disease in renal transplant is rare.*

**130. Answer is A (Haematuria):** *Harrisons 15th/ 1595, 2300; 16th/1691, 2331; 17th/1794, 2469 Harrison 18th/p 2351, 3213*

***Most patients with Alports syndrome present with haematuria.***
*Alport syndrome is the 'most common hereditary nephritis' and it is characterized by haematuria – Harrison*

**Manifestations**

| Renal manifestations | Extrarenal manifestations |
|---|---|
| - Microscopic haematuria | - Sensorineural hearing loss |
| - Proteinuria (nephrotic range – 30%) | - Bilateral anterior lenticonus (15 to 30%) |
| - Progressive renal insufficiency | - Recurrent corneal erosions |

- **Sensorineural deafness** is primarily in the high tone range and can frequently be detected only by an audiogram. It is thus unlikely to be a presenting symptom. (It is usually non progressive)
- **Proteinuria** by itself is again unlikely to be a presenting symptom.
- **Oliguria** would develop with progressively increasing renal insufficiency

**131. Answer is A (Alport's syndrome):** *API 6th/ 666*

*Alport is syndrome has not been mentioned to recur in kidney after a renal tansplant.*

**Disease associated with significant though varying recurrence rates in the graft include**

| Glomerulonephritis | Metabolic |
|---|---|
| - Membranoproliferative type II | - Type I Diabetes |
| - IgA nephropathy | - Amyloidosis |
| - Anti GBM disease (Good pastures) | - Oxalosis |
| - Focal segmental glomerulosclerosis (FSGS) | - Cystinosis |
| - Haematytic uraemic syndrome | |

## Minimal Change Nephropathy

**132. Answer is A (Fusion of foot processes of the glomerular epithelial cells):** *CMDT 2007/942; 2009/818; NMS medicine 6th/256, Harrison 18th/p 2345 Harrisons 17th/1790, Harrisons 16th/1684, 1685, Nelsons 17th/1754; Chandrasoma Tayler 3rd/705; Robbins 6th/956*

*The presence of generalized edema is a 7 year old boy with proteinuria suggests a diagnosis of Nephrotic syndrome. This child is likely to have. Minimal change disease as this is the most common cause of Nephrotic syndrome in children and is associated with normal findings on Light microscopy*

***Patients with minimal change disease characteristically show fusion of foot processes of the glomerular epethelial cells on electron microscopy.***

Minimal change Disease: Review

- Most common cause of Nephrotic syndrome in children (80% in children; 20% in adults)
- Peak Age of onset is between 6-8 years of Age (usually < 10 years)
- Type of onset : Insiduous

Clinical features

Peripheral Edema: Presenting Feature

Nephrotic syndrome is the typical presentation
Peripheral edema is the hallmark of Nephrotic syndrome occurring when serum albumin levels become less than 3g/dl
Initially dependent Edema $\xrightarrow{Later}$ Generalized edema
May develop Pleural effusion, pulmonary edema, ascitis

- Hematuria : 20-30%
- Hypertension : V. Rare
- Renal failure : Does not usually progress to renal failure

Laboratory (Features of Nephrotic syndrome)

- *Proteinuria*
- *Hypoalbuminemia*
- *Hyperlipidemia/Hyper cholesterolemia (Increased hepatic prduction of lipids)*
- *Hypercoagulability*

Renal pathology (Biopsy)

| Investigation | Observation |
|---|---|
| Light microscopy Q | No abnormality hence the term minimal change |
| Electron microscopy Q | Fusion of foot processes |
| Immunofluorescence Q | Absence of immunoglobulin or complement |

Prognosis

- *Prognosis is Good*
- *Response to steroids is Excellent*
- *Does not progress to Renal Failure*

Treatments

- *Corticosteroids form the mainstay for treatment of MCD*

**133. Answer is A (No IgG Deposits or C3 deposition on Renal biopsy)**

*The presence of generalized edema significant proteinuria and absence of hematuria in a young (7 year old) girl suggests a diagnosis of Nephrotic syndrome. Minimal change disease (Lipoid nephrosis) is the commonest cause of Nephrotic syndrome in children and is the most likely diagnosis of the patient in question.*

***Minimal change disease* is characterized by absence of IgG deposits and / or complement on immunofluorescence (biopsy specimen) and is therefore the single best answer of choice.**

***IgA Nephropathy and Alport's syndrome*** characteristically present with an Acute Nephritic syndrome with recurrent gross hematuria. The patient in question has no hematuria and hence these diagnosis can be excluded.
***Serum complement C3 levels*** are characteristically normal in Minimal change disease

The Patient in question is a case of Minimal change disease because:

| Age of Patient | Presenting symptoms | Laboratory Features |
|---|---|---|
| **Peak age of onset** of Minimal change disease is 6 – 8 years | **Peripheral edema / Generalized edema** is the characteristic presenting feature of minimal change disease. **Hematuria** is uncommon in Minimal change disease | • **Proteinuria** (Nephrotic range) is characteristic<br>• **Hyaline casts and Fatty casts** may be seen in minimal change disease. |

**Occasional Hyaline casts and Fatty casts may be seen in Minimal change disease**

*- Clinical Laboratory Medicine' by Ravel 6th /156*

| Hyaline Casts | Fatty Casts |
|---|---|
| • Hyaline casts are composed almost exclusively of protein alone and they pass almost unchanged down the urinary tract | • Fatty casts are a special type of cellular cast associated with fatty degeneration of tubular epithelium |
| • Small number of ***these casts may be seen in normal urine and in*** any condition associated with proteinuria (including Minimal change disease) | • These casts are composed of fatty droplets and protein |
| • These casts carry no attached significance and do not necessarily imply an underlying renal disease | • ***Presence of these casts suggests a disease associated with nephrotic syndrome such as primary lipoid nephrosis*** (minimal change) or nephrosis secondary to Diabetes, SLE, amyloidosis etc. |

**Minimal change Disease: Review**

- Most common cause of Nephrotic syndrome in children (80% in children; 20% in adults)
- Peak Age of onset is between 6-8 years of Age (usually < 10 years)
- Type of onset : Insidious

**Clinical features**

- ***Peripheral Edema: Presenting Feature***

  Nephrotic syndrome is the typical presentation
  Peripheral edema is the hallmark of Nephrotic syndrome occurring when serum albumin levels become less than 3g/dl
  Initially dependent Edema $\xrightarrow{Later}$ Generalized edema
  May develop Pleural effusion, pulmonary edema, ascitis

- ***Hematuria*** : ***Uncommon*** (may be seen in 20-30% of patients)
- Hypertension : V. Rare

**Laboratory (Features of Nephrotic syndrome)**

- *Proteinuria*
- *Hypoalbuminemia*
- *Hyperlipidemia/Hyper cholesterolemia (Increased hepatic production of lipids)*
- *Hypercoagulability*

***Serum Complement 'C3' levels are Normal***

Renal pathology (Biopsy)

| Investigation | Observation |
|---|---|
| Light microscopy $^{Q}$ | ***No abnormality*** hence the term minimal change |
| Electron microscopy $^{Q}$ | Fusion of foot processes |
| Immunofluorescence $^{Q}$ | ***Absence of immunoglobulin or complement*** |

***No immunoglobulin deposit (IgG) are seen as Renal biopsy***

Prognosis

- *Prognosis is Good*
- *Response to steroids is Excellent*
- *Does not progress to Renal Failure*

Treatments

*Corticosteroids form the mainstay for treatment of MCD*

**134. Answer is D (No change seen):** *Chandrasoma Taylor 3rd/ 705*

***No abnormality is evident on light microscopy in a case of minimal change disease.***

| Investigation | Observation |
|---|---|
| *Light microscopy* $^{Q}$ | *No abnormality hence the term minimal change* |
| *Electron microscopy* $^{Q}$ | *Fusion of foot processes* |
| *Immunofluorescence* $^{Q}$ | *Absence of immunoglobulin or complement* |

**135. Answer is A (No abnormality):** *Chandrasoma Taylor 3rd/705; Harrison 18th/p 2345 Harrisons 17th/1790; Harrisons 16th/1684, Nelsons 17th/1754*

***Light microscopy shows no abnormality in Minimal change Disease***

| Investigation | Observation |
|---|---|
| *Light microscopy* $^{Q}$ | *No abnormality hence the term minimal change* |
| *Electron microscopy* $^{Q}$ | *Fusion of foot processes / Effacement of foot process* |
| *Immunofluorescence* $^{Q}$ | *Absence of immunoglobulin or complement* |

**136. Answer is A (Appears normal under light microscope but Electron microscope shows loss of foot processes) -** *Robbins 6th/ 954 Refer previous question; Robbins 7th/981*

- ***It is characterised by diffuse loss of foot processes of epithelial cells, which however, is detectable by electron microscopy only; Glomeruli appear normal by Light microscopy.***
- No electron dense deposits are seen in minimal change disease. Mesangial deposits are a feature of mesangio-proliferative G.N. eg. Ig A nephropathy.
- Tram-track appearance is a feature of membrano-proliferative G.N.
- Haematuria is not a feature of minimal change disease. Gross haematuria is seen in glomerulonephritis that cause acute nephritic syndrome eg. post streptococcal G.N. and IgA G.N.

**137. Answer is A (Glomerular function is lost due to loss of polyanions around the foot processes) :** *Heptinstall's pathology of kidney 6th/128, Clinical Pediatric Nephrology 2nd/6 ; Harrison 18th/p 2345 Harrisons 17th.1790: Harrisons 16th/1684, 1685*

***Loss of polyanionic charge is believed to be the main cause for loss of glomerular function (albuminuria) in minimal change disease***

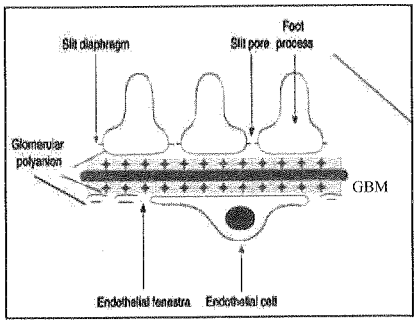
*Loss of polyanions is believed to result in effacement of foot processes and development of proteinuria in minimal change disease*

**Mechanism of Proteinuria in Minimal change Disease (MCD) (Heptinstall's)**

Effacement of foot process (Earlier called fusion of foot process) is believed to play an important role in causes proteinuria in MCD.

The mechanisms responsible for fusion /effacement of foot processes include:

- ***Loss of negative charge (Loss of Polyanions)***
- *Disruption of components of slit diaphragm (Demonstrated in congenital nephrotic syndrome of the Finnish type)*
- *Loss of actin cytoskeleton*
- *Detachment of the podocyte from the GBM.*




**Note**

*Minimal change disease is characterized by diffuse effacement of foot process 'diffuse effacement of foot process is synonymous with fusion of foot processes.*

**138. Answer is A, D (Normal light microscopy; Effacement of foot process):** *Harrison 18th/p 2345 Harrison 17th /1790*

***Minimal Change Disease or Lipoid Nephrosis is typically charachterized by a normal light microscopy and effacement of foot processes on electron microscopy***

*'MCD on renal biopsy **shows no obvious glomerular lesion by light microscopy** and is negative for deposits by immunofluorescent microscopy, or occasionally shows small amounts of IgM in the mesangium. **Electron microscopy, however consistently demonstrates an effacement of the foot process** supporting the epithelial podocytes with weakening of slit-pore membranes.'- Harrison's 17th / 1790*

**FSGS may be seen in the small subset of patients with steroid resistance but its presence is not a typical feature of Lipoid Nephrosis**

*'Patients with steroid resistance can develop FSGS on repeat biopsy'- Harrison's 17th/ 1790*

**139. Answer is A (Hypertension):** *Harrison 18th/p 2345 Harrison 17th/, 1790; Ghai 5th / 370; Ghai 6th/451*

***Hypertension is not a feature of nephrotic syndrome and is rare in Minimal change disease.***

Edema and *Selective proteinuria are features of nephrotic syndrome. Fever may be present on account of increased susceptibility to infection.*

***Minimal Change Disease** is the most common cause of Nephrotic syndrome in children.*

***Hypertension is not a feature of nephrotic syndrome and is rare in Minimal change disease.***

| Features | Minimal Change Disease |
|---|---|
| Light Microscopy | Minimal Change / No significant abnormalities |
| Electron microscopy | Obliteration of epithelial foot processes |
| Immunofluorescence | No deposits of immune reactants |
| Serum complements | *Levels are normal* Q |
| Age of onset | *Mainly below 6 years* Q |
| Type of Onset | *Insidious* Q |
| Hematuria | *Rare* Q |
| Hypertension | ***Rare*** Q |
| Edema | *Presenting feature* Q |
| Proteinuria | *Present (mainly Albumin)* Q |
| Response to steroids | *Excellent (Abolition of proteinuria)* Q |
| Prognosis | *Good* Q |

**140. Answer is A (Hepatitis B):** *Harrison 16th/1685 (Tab. 264-3); Harrison 17th/ 1790 Harrison 18th/p 2345*

***'Hepatitis B' has not been mentioned to have any association with minimal change disease'.***

**Major Causes of Minimal Change Disease / (Nil) disease / Lipoid Nephrosis**

| Idiopathic | In association with systemic diseases or drugs[q] |
|---|---|
| | ***HIV infection***[Q]<br>***Hodgkins disease***[Q] and other Lymphoproliferative malignancies<br>***Drug induced Interstitial Nephritis***[Q]<br>NSAIDS<br>Rifampicin<br>Interferon α |

**141. Answer is B (Minimal Change Glomerulonephritis) :** *See above*

*Steroids produce on excellent response in minimal change disease and remission has been found to occur in 75% pediatric patients. (Judged as an abolition of proteinuria) – Ghai 5th / 370*

## Diabetic Glomerulopathy

**142. Answer is B (Diffuse glomerulosclerosis):** *Robbins 6th/ 966; 7th/991; Harsh Mohan Pathology 5th/701*

*Diffuse glomerular lesions are the most common – Harsh Mohan*

**The morphological changes in Glomeruli is diabetic glomerulosclerosis include:**

| Capillary basement membrane thickening | Diffuse glomerulo sclerosis | Nodular glomerulo sclerosis |
|---|---|---|
| "The earliest morphological abnormality in diabetic nephropathy is thickening of basement membrane" (and expansion of mesangium due to accumulation of extracellular matrix) | "Diffuse glomerular lesions are the most common".<br>*– Harsh Mohan 7th/701* | also called intercapillary glomerulosclerosis or kimmetstiel – Wilson disease. Are virtually pathognomic of diabetes (most specific) *- Robbins 6th/ 967.* |

**143. Answer is C (Microalbuminuria):** *Harrison 17th /2288; 'Hypertenson primer' by Tzzo (Lippincott Williams & Wilkins) 2008 4th/384; 'Starnberg's Diagnostic surgical pathology 4th/1890; 'General Surgery Principles and International practice' (Springer) 2008/322*

***The first clinically detectable sign of diabetic nephropathy is microalbuminuria.***

*'The first clinically detectable sign of diabetic nephropathy is microalbuminuria'.*

*- General Surgery Principles & International Practice 2008/522*

*'The first sign of diabetic renal disease is microalbumin in the urine'-'Management of Diabetic Mellitus' 6th (Springer)/359*

**Microalbuminuria and Diabetic Renal Disease**

- *Microalbuminuria is the first clinically detectable sign of diabetic nephropathy*
- Microalbuminuria refers to excretion of albumin in the urine in amounts that are abnormal but below the limit of detection of conventional urine dipsticks[Q]

  *Microalbuminuria is defined as excretion of 30-300 mg of albumin/day in a 24 hour collection[Q] or 30-300μg/mg[Q] creatinine in a spot collection.*
- The presence of albumin in the urine in the range of microalbuminuria is *best determined by a urinary Albumin/Creatinine ratio in a spot voided urine (Prefered method for delecting microalbuminuria)*[Q]
- *Microalbuminuria is best detected by Sensitive Radioimmuneassays*[Q]
- The recognition of microalbuminuria in patients with diabetes mellitus allows identification of diabetic nephropathy and institution of treatment to reduce the risk of progressive kidney disease at an earlier stage than would be possible with conventional urine dip-sticks

  There is clear evidence that the detection of early diabetic nephropathy manifested by microalbuminuria is responsive to antihypertensive therapy in particular the use of ACE Inhibitors or Angiotensin Receptor Blockers.

**Stages of Diabetic Nephropathy according to Mogensen:**

| Stage | Duration of diabetes | Clinical, biological and pathological signs related to renal disease |
|---|---|---|
| 1 | At diagnosis | • *No clinical or biological signs of renal injury*<br>• *Hypertrophy of the kidneys*<br>• *Glomerular hyperfiltration* |
| 2 | 2-5 years | *Clinically and biologically 'silent' nephropathy* |
| 3 | 5-10 years | **Early nephropathy:**<br>• ***Microalbuminuria***<br>• *High blood pressure*<br>• *Normal GFR* |
| 4 | 10-20 years | **Established diabetic nephropathy:**<br>• ***Macroalbuminuria***<br>• *High blood pressure*<br>• *Decreasing GFR*<br>• *Pathology: mesangial expansion; GBM thickening; and glomerular sclerosis* |
| 5 | >20 years | **End-stage renal disease**<br>• *Pathology: advanced fibrosis of the kidneys*<br>Need for:<br>• *Renal transplant (± pancreas)*<br>• *Peritoneal dialysis*<br>• *Hemodialysis* |

**144. Answer is A (Microalbuminuria):** *Repeat*

***The first clinically detectable sign of Diabetic Nephropathy is Microalbuminuria.***

**145. Answer is C (Urinary A/C Ratio in a spot voided sample):** *'Hypertension Primer' 4th/384*

***The preferred method to establish microalbuminuria is to determine Albuma / Creatinine Ratio (A/C Ratio) in a spot voided urine sample.***

*'The presence of albumin in the urine in the range of microalbuminuria is best determined by a urinary A /C Ratio in a spot voided sample. The A/C ratio correlates closely with 24 hour urine albumin estimation and this measure has the advantage of avoiding in accuracies in urine collection and the unpleasentness of having to store urine during the collection process'- Hypertension Primer' 4th/384*

**146. Answer is C (Focal sclerosis):** *Harsh Mohan 4th / 662*

***Focal sclerosis has not been mentioned as a characteristic feature of Diabetic Nephropathy.***

**Glomerular Lesions in Diabetes**

| Diffuse glomerulosclerosis: | Nodular glomerulosclerosis |
|---|---|
| • Is the ***most common pattern of involvement***$^{Q}$<br>• The most common pathological change is ***thickening of glomerular basement membrane***$^{Q}$ which occurs virtually in all diabetics and is part and parcel of diabetic microangiopathy<br>• Various exudative lesions such as capsular hyaline drops or 'fibrin caps' may be present<br>• ***Capsular drop***$^{Q}$: is an eosinophilic thickening of parietal layer of Bowman's capsule and bulges into glomerular space<br>• ***Fibrin caps***$^{Q}$ : is a homogeneous eosinophilic material appearing on the wall of a peripheral capillary of a lobule | • Is virtually ***pathognomic***$^{Q}$ ***of diabetes mellitus***<br>• Is also called ***Kimmelstiel-Wilson lesion*** *or* ***Intercapillary glomerulosclerosis***$^{Q}$<br>• The pathological change consist of one or more nodules in a few or many glomeruli<br>• Uninvolved lobules and glomeruli all show striking diffuse glomerulosclerosis<br>*Focal sclerosis has not been mentioned in the entire description on diabetic nephropathy and therefore is the answer of exclusion.* |

**147. Answer is C (Strict glycemic control, Low protein Diet, ACE Inhibitors):** *Harrison 17th /2288*

***Recommended intervention for early diabetic nephropathy manifested by microalbuminuria include glycemic control, strict blood pressure control, ACE Inhibitors/ARB and low protein diet.***

**The Recommendation for treatment of early diabetic nephropathy** manifested by microalbuminuria is to delay the progression from microalbuminuria to macroalbuminuria

**Effective Recommended Interventions in diabetic patients with microalbuminuria**

- *Immproved Glycemic control (Normalization of glycemia)*
- *Strict Blood Pressure Control (Blood pressure aim < 125/75)*
- *ACE Inhibitors and/or Angiotensin Receptor Blockers*
  *(Provide drug specific benefit independent of blood pressure control)*
- *Modest Reduction in Protein Intake (0.8g/kg /day)*

## HIV Glomerulopathy

**148. Answer is A (FSGN):** *Harrison 18th/p 2353 Harrisons 17th/ 1796*

***The most charachteristic Glomerulopathy in HIV is focal segmental Glomerulosclerosis (FSGS) which typically reveals collapse of the glomerular capillary tuft called collapsing glomerulopathy.***

*HIV associated Nephropathy is severe rapidly progressive collapsing form of FSGS*

**149. Answer is A (Focal Segmental Glomerulosclerosis):** *Harrison 18th/p 2353 Harrisons 17th/ 1796*

***The most characteristic glomerulopathy in HIV is Focal Segmental Glomerulosclerosis (FSGS) which typically reveals collapse of the glomerular capillary tuft called collapsing glomerulopathy.***

*HIV associated Nephropathy is a severe rapidly progressive collapsing form of FSGS.*

**150. Answer is C (Collapsing glomerulopathy):** *Harrison 18th/p 2353 Harrisons 17th/1796*

***The most charachteristic glomerulonephritis in HIV is focal segmental Glomerulosclerosis (FSGS). The FSGS characteristically reveals collapse of glomerular capillary tuft and is called collapsing glomerulopathy.***

**151. Answer is D (Hypertrophy of visceral epithelium cells) :** *Robbins 7th/983 Pediatric Nephrology (2003)/486*

***The charachteristic feature of collapsing glomerulopathy are collapse of glomerular tuft and proliferation and hyperplasia of glomerular visceral epethelial cells. Amongst the options provided Hypertrophy of visceral epethelial cells is the single best answer of choice.***

*'A charachteristic feature of collapsing glomerulopathy is proliferation and hypertrophy of visceral epithelial cells'*
*- Robbins 7th/983*

According to working Classification of FSGS (Pediatric Nephrology)

| Type of FSGS | Key Histological Feature | Prognosis |
|---|---|---|
| Collapsing FSGS | *Collapse of Tuft*<br>*Glomerular visceral Epethelial cell Hyperplasia (GVEC hyperplasia)* | Poor |

*Option A in question mentions 'tuft necrosis' and not collapse of tuft hence option D becomes the single best answer of choice.*

## Lupus nephritis

**152. Answer is C (Wire loop lesions):** *Robbin's 7th/232; Harrison 18th/p 2727 Harrison 17th/2077; Fundamentals of Renal Pathology (2006) 1st/85*

***Wire loop lesions are characteristic of Lupus nephritis.***

**Wire loop lesions:**

- Wire loop lesions represent local PAS – Positive thickening of glomerular capillary walls and are characteristically seen in Lupus Nephritis (SLE)
- These lesions result from subendothelial deposits between endothelium and basement membrane. When extensive and confluent, these subendothelial deposits create a homogenous thickening of the capillary wall which can be seen in light microscopy as 'Wire loop lesion'

- Wire loop lesions are most characteristic of Lupus Nephritis Class IV or Diffuse Lupus Nephritis
  These may however also be seen in Class III (Focal Lupus Nephritis) and Class V (membranous) Lupus Nephritis.

| Wire Loop Lesion (Lupus Nephritis) | |
|---|---|
| Most characteristic of: | Also seen in: |
| ***Lupus Nephritis Class IV*** *(Diffuse Lupus Nephritis)* | *Lupus Nephritis Class III (Focal) > Lupus Nephritis Class V (Membranous)* |

**153. Answer is C (Diffuse Proliferative Glomerutonephritis);** *Sternberg's Diagnostic surgical pathology 4th/1910,1911*

*Heptinstall's Pathology of the kidney 6th/546,547; Diseases of the kidney and Urinary Tract 8th/1688; Harrison 18th/p 2727 Harrisons 17th/2076, 2077, 2078; Harrisons 16th/1961,1963*

***Wire loop lesions are most charachteristic of diffuse proliferative glomerulonephritis (Class IV WHO) but may also be seen in focal proliferative glomerulonephritis (Class III WHO).***

| Wire Loop Lesion (Lupus Nephritis) | |
|---|---|
| Most characteristic of: | Also seen in: |
| ***Lupus Nephritis Class IV*** *(Diffuse Lupus Nephritis)* | *Lupus Nephritis Class III (Focal) > Lupus Nephritis Class V (Membranous)* |

**154. Answer is D (Anti – LA (SSB)):** *Samter's Immunologic disease 6th/497; 'Systemic Lupus Erythematosis' 4th/894*

*Presence of Anti – LA (SSB) in SLE suggests concomitant Sjogren's syndrome. In SLE, patients with concomitant Sjogren's syndrome have a lower frequency of glomerulonephritis and a relatively good prognosis – Samter's Immunologic Diseases 6th/497*

| Factors associated with Adevrse Prognosis and High Risk of Renal Progression in Lupus Nephritis |
|---|

Demographic

- *Black race*
- *Hispanic ethnicity*
- *Male gender*
- *Extremes of age at onset of SLE*
- *Limited access to health care*

Clinical

- *Hypertension*
- *Severe extrarenal (especially neuropsychiatric) lupus activity*
- *Failure to achieve remission or marked delay to renal remission*
- *Pregnancy*

Laboratory

- *Nephritic urinary sediment*
- *Azotemia*
- *Anemia*
- *Thrombocytopanea*
- *Thrombotic microangiography (with or without anti-phospholipid antibodies)*
- ***Hypocomplementemia (especially falling levels)***
- ***High anti- ds DNA (especially rising titres)***
- *Persistent severe nephritic syndrome (artherosclerotic and thrombotic diathesis)*

Renal pathology

*Contracted kidney size*

*Proliferative glomerulonephritis (WHO class III, IV)*

*Mixed membranous (V) and proliferative (III-IV) glomerulonephritis*

*Cellular crescents (>25% of glomeruli)*

*Fibrinoid necrosis (>25% of glomeruli)*

*Very high activity index*

*Moderate-to-high chronicity index*

*Combinations of active (cellular crescents) and chronic features (interstitial fibrosis)*

*Extensive subendothelial deposits*

---

Note:

*The presence of Anti-RO or Anti-La antibodies in a pregnant woman is associated with a chance of 'neonatal lupus' developing in the infant (1-5%)*

*This may present in the fetus as a congenital heart block or neonatal lupus rash.*



## Amyloid Nephropathy

**155. Answer is B (Amyloid Nephropathy):** *Harrison 18th/945; 'Essentials of Nephrology' by Visveswaran 2nd/330; European Respiratory Monograph (European Respiratory Society) 2011/156*

***Secondary / Reactive Amyloidosis is an established typical complication of chronic conditions like bronchiectasis.*** Secondary amyloidosis is typically distributed in solid abdominal viscera like the kidney, liver, spleen and adrenals. *Kidneys are the most frequently affected organs.* ***Renal Amyloidosis is an established cause of secondary glomerular disease from chronic conditions like bronchiectasis and presence of edema on legs and proteinuria in a patient with chronic bronchiectasis should auggests the possibility of secondary/reactive renal amyloidosis.***

*'Renal Amyloidosis is usually manifested as proteinuria, often in the nephrotic range and associated with significant hypoalbuminemia, and edema or anasarca' – Harrison 18th/947*

| *Bronchiectasis is the most common respiratory disease underlying AA Amylodosis in the UK.* |
|---|

## Leprotic Glomerulopathy

**156. Answer is B (MPGN):** *Rooks Dermatology 5th/ 1073;*

***'Chronic renal failure in leprosy is commonly due to proliferative glomerulonephritis, interstitial nephritis and renal amyloidosis and is a common cause of death'*** *– Rooks*

*Remember however that most other infectious causes lead to membranous glomerulonephritis rather than MPGN.*

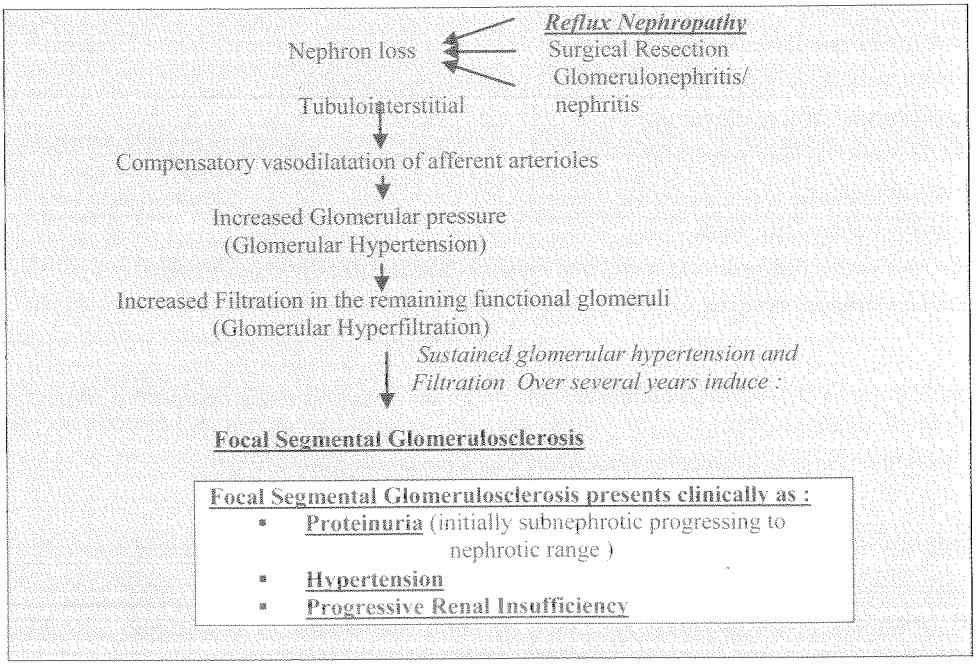
## Miscellaneous Glomerulonephritis

**157. Answer is B (Focal segmental Glomerulosclerosis):** *Harrison 16th/1686,1679; Midline References Robbins 7th/973, 1000*

***Focal segmental glomerulosclerosis may develop following acquired loss of nephrons from reflux nephropathy. Proteinuria is nonselective in most cases and may be in subnephrotic range (nephritic range < 3.0 g/24h) or nephrotic range.*** *- Harrison*

***Association of Reflux Nephropathy and proteinuria suggests an irreversible glomerular lesion most commonly focal segmental glomerulosclerosis : Medline***

**Association of Reflux Nephropathy / Focal Segmental Glomerulosclerosis and Proteinuria**




**158. Answer is C >B ( Membranoproliferative Glomerulonephritis > Mixed cryogloulinemia):**
*-Harrison 16th / 1682. 2012; 17th/2129; Harrison 18th/p 2798, 2799 CMDT 2006 / 925; 2009/821*

*The association of generalized edema, hypertension ,proteinuria, hematuria along with hypocomplimentemia and positive anti-hepatitis C antibodies may be seen in both Membranoproliferative Glomerulonephritis and Mixed Cryoglobulinemia.* ***With the limited information provided in question MPGN appears to be a better option in comparison to Essential Mixed Cryoglobulinemia for the following reasons:***

- *Cryoglobulinemic Glomerulopathy is most common with the Mixed Cryoglobuliinemias Type II and III which are most common in females and begin in the sixth decade. – Harrison 16tth / 1682*
  ***The patient in question is a male in the 4th decade of life ( 30 years )***
- *Most patients with cryoglobulinemia present with variable combination of stress ulceration, arthralgia, fatigue and Raynaud's phenomenon other than renal manifestations. The fundamental finding is presence of circulating cryoprecipitates.*

  ***The patient in question is not presenting with any of the above features to favour Mixed Cryoglobulinemia over MPGN.***
- ***Membranoproliferative glomerulonephritis is responsible for 80% of all Renal lesions in Essential Mixed Cryoglobunemia.*** *-Harrison 16th / 2012*

| Hepatitis C infection and Glomerular lesions (CMDT 06/924) |
|---|
| **Three clinicopathologic glomerular syndromes associated with hepatitis C are** :<br>• *Secondary MPGN*<br>• *Cryoglobulinemic Glomerulopathy*<br>• *Membranous nephropathy* |
| ***MPGN is the most common lesion****. These patients typically have haematuria, hypertension, proteinuria and anemia. Hypocomplementemia is very common with C4 typically more reduced than C3.* |

| Low complement level nephritis syndromes |
|---|
| ***(Immune complex glonerulonephritis)***<br>• *Idiopathic proliferative glomerulonephritis*<br>• *Crescentric glomenelonephritis*<br>• *Membranoproliferative glomerulonephritis*<br>• *Lupus nephritis*<br>• *Cryoglobulinemia*<br>• *Bacterial endocarditis*<br>• *Shunt nephritis*<br>• *Post infectious glomerulonephritis (post streptococcal)* |

159. **Answer is B > C (Essential mixed cryoglobulinemia > Membranoproliferative glomerulonephritis)**
*Harrison 18th/p 2798, 2799 Harrison 17th/2129; previous question*

***The presence of skin ulceration on clinical examination in a female patient around the 6th decade favors a diagnosis of Essential Mixed Cryoglobulinemia over MPGN.***
***Nevertheless if Essential Mixed Cryoglobulinemia is not amongst the options MPGN would be the single best answer of choice.***
***Membranoproliferative glomerulonephritis is a responsible for 80% of all renal lesions in essential mixed cryoglobulinemia.***

160. **Answer is A (Post streptococcal glomerulonephritis)**: *Harrison's 16th/1680; Harrison 17th / 1786, 1787; not et Harrison 18th/p 2340*

***Although all conditions mentioned in the question are associated with low compliment levels 'persistently depressed levels' are not seen in post streptococcal glomerulonephritis.***

***In post streptococcal glomerulonephritis:*** *serum $C_3$ levels are depressed within 2 weeks, however these usually return to normal levels within 6 to 8 weeks*

***Persistently depressed levels after this period should suggest another cause*** *such as presence of $C_3$ nephritic factor (Membranoproliferative glomenulonephritis) – Harrison*

***Differential diagnosis of Nephritic syndromes based on complement levels***

| *Low complement levels* | *Normal complement levels* |
|---|---|
| ***(Immune complex glonerulonephritis)*** | • ***Anti GBM disease:*** *Good posture's syndrome* |
| • *Idiopathic proliferative glomerulonephritis* | • ***Pauci*** *immune* ***glomenulonephritis*** |
| • *Crescentric glomenelonephritis* | - *Wegeners granulomatoses* |
| • *Membranoproliferative glomerulonephritis* | - *Microscopic polyarteritis nodosa* |
| • *Lupus nephritis* | • *Immune* ***complex mediated*** |
| • *Cryoglobulinemia* | - *IgA Nephropathy* |
| • *Bacterial endocarditis* | - *Henoch schonlein purpura* |
| • *Shunt nephritis* | - *Fibrillary Glomerulonephritis* |
| • *Post infectious glomerulonephritis (post streptococcal)* | |

161. **Answer is C (Diarrhea associated hemolytic uremic syndrome):** *Refer previous question; Harrison 16th/1680*

*Lupus Nephritis, post streptococcal glomerulonephritis and membrano proliferative glomerulonephritis are all associated with low complement levels as depicted in the table in the previous question.* ***Depressed complement levels are not seen in HUS***
**Hemolytic uraemic syndrome** is characterized by microangiopathic hemolytic anemia, thrombocytopenia and renal failure due to microangiopathy.

**Depressed complement levels are not seen and laboratory features include:**
- Thrombocytopenia
- Normal tests of coagulation with exception of elevated fibrin degradation products
- Microangiopathic hemolytic anemia: striking red blood cell fragmentation on peripheral blood smear
- *LDH elevation, out of proportion to degree of hemolysis.*

162. **Answer is A, D and E (PSGN, MPGN and Infective endocarditis):** *Refer previous question*

***PSGN, MPGN and Infective endocarditis are associated with depressed complement levels or Hypocomplementemia.***

**163. Answer is B (Mesangiocapillary Glomerulonephritis) :** *Harrison 18th/p 2344 Harrisons 17th /1789, Chandrasoma Taylor 3rd /708*

*Mesangiocapillary Glomerulonephritis is the other name for Membranoproliferative glomerulonephritis. It is a type of proliferative Glomerulonephritis. (Harrisons 17th /1789)*

**Proliferative changes in Glomerulonephritis** *(Refer: Chandrsoma Taylor 3rd /702, 708)*

- Glomerulus contains Endothelial cells, Epithelial cells, and Mesangial cells. Any of the three cell types may undergo proliferation in different types of Proliferativ Glomerulonephritis.
- Proliferative changes are not limited to Membranoproliferative and Mesangioproliferative Glomerulonephritis, but may be seen in several other forms of Glomerulonephritis

**Glomerulonephritis and Proliferative changes**

**Glomerulonephritis without proliferative changes**

| *Glomerulonephritis* | *Proliferative changes* |
|---|---|
| Minimal change Disease | - (Absent) |
| *Membranous Glomerulonephritis* | - (Absent) |
| Diabetic Nephropathy | - (Absent) |
| *Amyloidosis* | - (Absent) |
| *Focal segmental Glomerulosclerosis* | ± *Variants with proliferative lesions have been described including cellular lesions with endocapillary hypercellularity- (Harrisons)* |

**Glomerulonephritis with proliferative changes**

| *Glomerulonephritis* | *Proliferative changes* |
|---|---|
| *Post streptococcal GN* | *+ (Crescents)* |
| *Antibasement membrane disease (Good – pasture's syndrome)* | *+ (Crescents)* |
| *IgA Nephropathy (Berger's)* | *+ (Mesangial)* |
| *Henoch Schonlein Purpura* | *+ (Mesangial)* |
| *Mesangioproliferative GN* | *+ (Mesangial)* |
| *Membranoproliferative GN* **(Mesangiocapillary GN)** | *+ (Endothelial & Mesangial)* |
| *Focal Glomerulonephritis* | *+ (Focal)* |
| *Secondary Glomerulonephritis SLE / PAN* | *+ Variable* |

*Note : Crescents represent proliferation of epethelial cells*

**164. Answer is C (IgA Nephropathy):** *Chandrasoma Taylor 2nd/703*

*Proliferative glomerular deposits are characteristic of IgA nephropathy.*

*Diabetes, Amyloidosis and membranous glomerulonephritis are not associated with proliferative changes.*

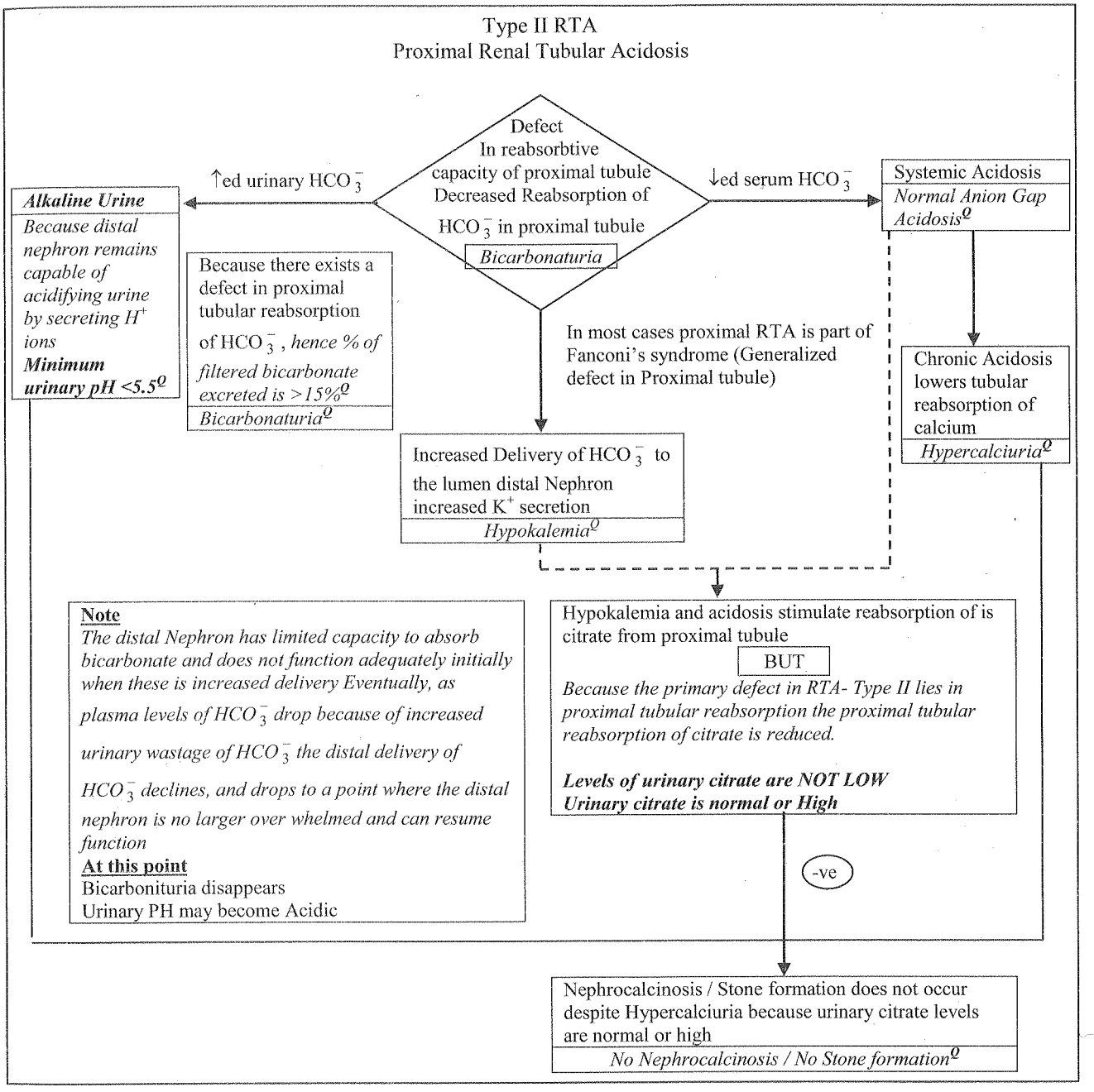
| Type | Proliferative | Membranous | Diffuse/Focal |
|---|---|---|---|
| *IgA Nephropathy* (Mesangial) | +ve | -ve | Diffuse |
| *Membranous GN* | -ve | +ve | Diffuse |
| *Diabetic Nephropathy* | -ve (Focal sclerosis) | +ve | Diffuse/Focal |
| *Amyloidosis* | -ve | +ve | Diffuse |

## Renal Tubular Acidosis

**165. Answer is C (Decreased Urinary citrate):** *Harrisons 16th/1699*

*Type II RTA is associated with normal or increased urinary citrate*

*'Urine citrate levels are normal or high because of reduced proximal tubular reabsorption of citrate' – Harrisons*

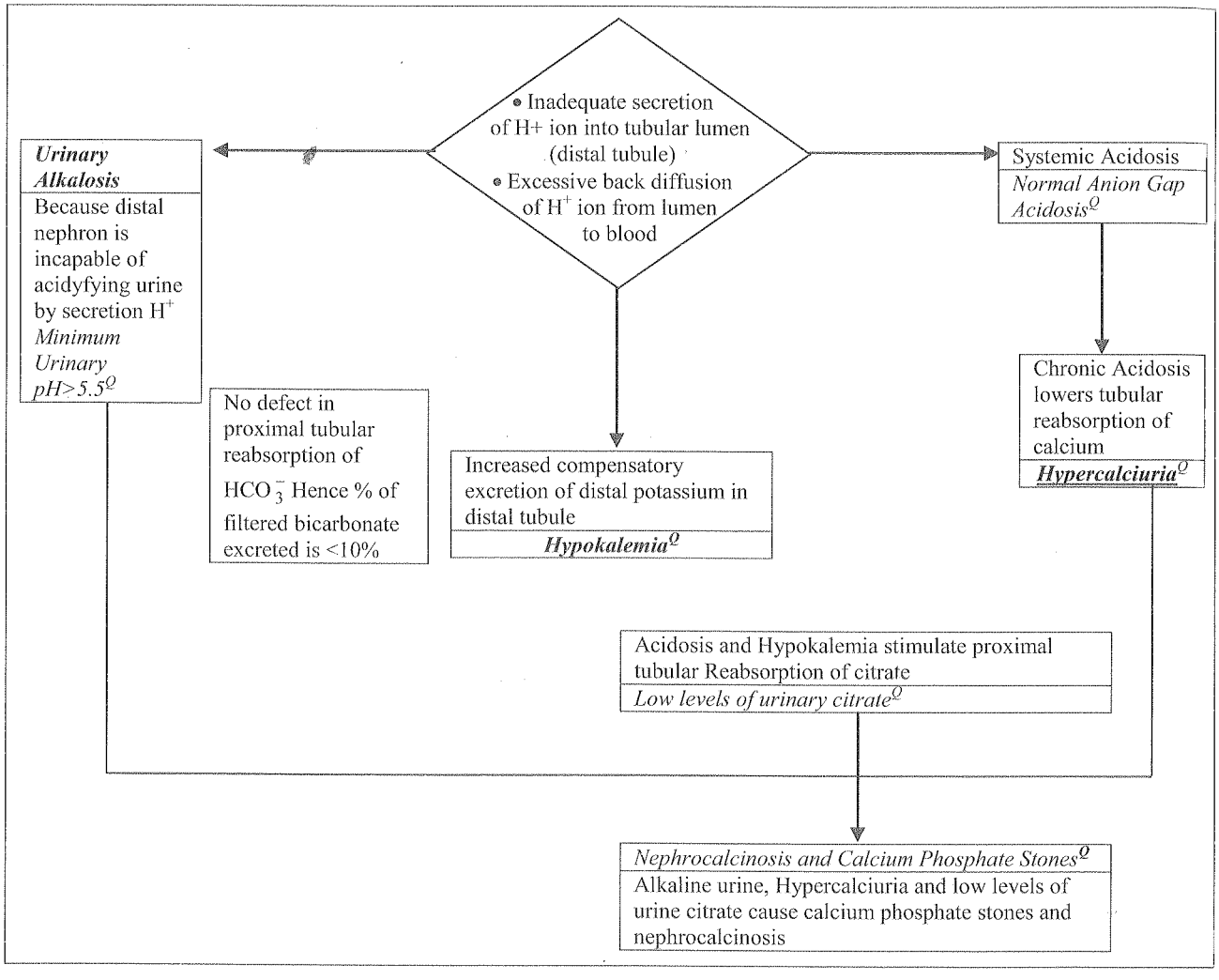



**166. Answer is D (↑ Urinary citrate):** *Harrisons 16th/1698, 1699*

*Type I Renal Tubular Acidosis is associated with low levels of urinary citrate*

*Urinary citrate excretion is low as hypokalemia and acidosis stimulate proxmal tubular reabsorption of citrate.*

Type I RTA
Distal Renal Tubular Acidosis




**167. Answer is C (Associated with Hyperkalemia):** *Harrison 18th/2364*

***Type I RTA is associated with Hypokalemia and not Hyperkalemia.***
*Type I and Type II RTA are both associated with hypokalemia. Hyperkalemia is a feature of Type IV Renal Tubular Acidosis.*

**Type I (Distal) RTA is associated with Hyperkalemia, failure to acidify urine to a pH of <5 and an increased risk of urinary stones**

| Feature | Type I | Type II | Type IV |
|---|---|---|---|
| *Normal anion gap* | *Yes* | *Yes* | *Yes* |
| ***Minimum urine pH*** | ***> 5.5*** | *< 5.5* | *< 5.5* |
| *% Filtered bicarbonate excreted* | *< 10* | *> 15* | *< 10* |
| ***Serum potassium*** | ***Low*** | ***Low*** | ***High*** |
| *Fanconi syndrome* | *No* | *Yes* | *No* |
| ***Stones / Nephrocalcinosis*** | ***Yes*** | *No* | ***No*** |
| *Daily acid excretion* | *Low* | *Normal* | *Low* |
| *Urinary anion gap* | *Positive* | *Positive* | *Positive* |

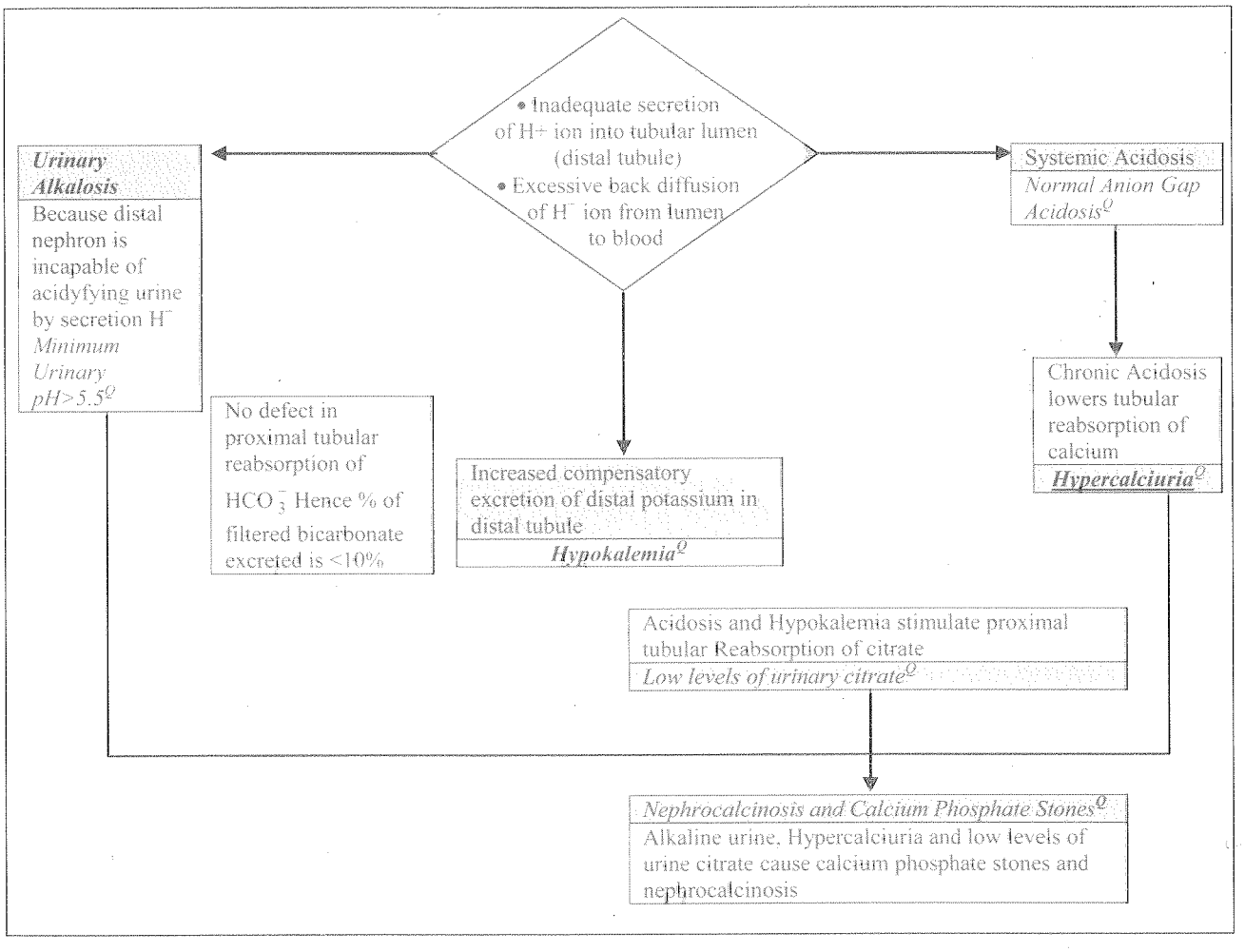
*Type I RTA is associated with failure to acidify urine to a pH <5 because distal nephron is incapable of acidyfying urine by secretion of $H^+$(Minimum Urinary pH>5.5Q)*

**Treatment of Type I (Distal) RTA involves alkali replacement with bicarbonate**

***Early initiation of alkali replacement at doses equivalent 1-3 mmol/kg per day of bicarbonate in divided doses*** will usually correct the acidosis, hypokalemia and hypocitraturia maintaining growth and preventing bone disease in early onset dRTA.

*Citrate is generally tolerated better than sodium bicarbonate and can be given as the potassium or sodium salt depending on degree of hypokalemia.*

Type I RTA
Distal Renal Tubular Acidosis




**168. Answer is C (Calcium Stones):** *Refer Renal Tubular Acidosis Algorithm*

***Distal Renal Tubular Acidosis is associated with increased in cadence of Calcium Phosphate Stones*** *Alkaline urine, Hypercalciuria and low levels of urinary citrate precipitate calcium phosphate stones in the kidney in patients with Distal Renal Tubular Acidosis (Type1).*

*Proximal Renal Tubular Acidosis (Type-2) is not associated with increased incidence of Renal Stones despite Hypercalciuria because urinary citrate levels are normal or high.*

**169. Answer is B (Hypokalemia):** *Harrison 16th/1699; Harrison 17th/1805; Harrison 18th/p 2364, 2365*

***Both type I and type II RTA, are associated with Hypokalemia. Hypokalemia therefore cannot be used to differentiate between Type I and Type II RTA.***

| Feature | Type I | Type II | Type IV |
|---|---|---|---|
| *Normal anion gap* | *Yes* | *Yes* | *Yes* |
| *Minimum urine pH* | *> 5.5* | *< 5.5* | *< 5.5* |
| *% filtered bicarbonate excreted* | *< 10* | *> 15* | *< 10* |
| ***Serum potassium*** | ***Low*** | ***Low*** | *High* |
| ***Fanconi syndrome*** | ***No*** | ***Yes*** | *No* |
| ***Stones / Nephrocalcinosis*** | ***Yes*** | ***No*** | ***No*** |
| ***Daily acid excretion*** | ***Low*** | ***Normal*** | *Low* |
| *Urinary anion gap* | *Positive* | *Positive* | *Positive* |

**170. Aswer is D (Fanconi syndrome):** *See previous question; Harrison 16th/1699,267; 17th/1805; 18th/p 2364, 2365 Kumar & Clarke 5th/1116*

***Fanconi syndrome occurs in renal tubular acidosis type II.***

| Feature | Type I RTA | Type II RTA | Type IV RTA |
|---|---|---|---|
| Fanconi syndrome | No | Yes | No |

**Fanconis Syndrome** *is an entity characterized by defective tubular reabsorption of most amino acids, glucose. urate, phosphate and bicarbonate. Defective tubular absorption of bicarbonate, with failure to transport hydrogen ions* ***causes a renal tubular acidosis*** *producing hyperchloremic acidosis.*

***Proximal RTA (RTA type II)*** *is most often due to generalized proximal tubular dysfunction manifested by glycosuria aminoaciduria and phosphaturia (Fanconi's Syndrome) – Harrisons*

**171. Answer is C (Renal Tubular Acidosis):** *Harrison 18th/368, 369; 17th/292; Washington Manual of Critical Care (2007)/182*

***Positive Urinary Anion gap helps in establishing a diagnosis of Renal Tubular Acidosis.***

*Urinary Anion Gap (UAG) can be used to estimate renal ammonium production and distinguish Renal Tubular Acidosis (Positive UAG) from G1 bicarbonate loss (Negative UAG)- Harrisons*

**Urinary Anion Gap (UAG)**

- Urinary Anion Gap (UAG) calculation is useful in cases of *Normal Anion Gap (Hyperchloremic) Metabolic Acidosis*
- Normal Anion Gap Acidosis may result from excessive bicarbonate losses from either the gastrointestinal tract (eg diarrhea) or renal sources (eg Renal Tubular Acidosis)
- *Urinary Anion Gap Estimation helps to distinguish Renal bicarbonate loss from Gastrointestinal bicarbonate loss thereby helping in establishing the cause of normal anion gap metabolic acidosis*

> ***Positive Urinary Anion Gap: Implies Renal loss of Bicarbonate and the diagnosis is usually distal RTA***
> ***Negative Urinary Anion Gap: Implies Gastrointestinal loss of Bicarbonate***

Note

*In type II (Proximal RTA) the kidney has defective HCO3- reabsorption leading to increased HCO3- excretion rather than decreased NH4Cl excretion. Thus the urinary anion gap is often negative*

| Urinary Anion Gap |
|---|
| Urinary Anion Gap (UAG) is defined by the difference between major urinary cations and major urinary anion<br>UAG = (Urine Na+ + Urine K+ ) – Urine Cl-<br>*Normally / Typically the UAG is nearly zero or slightly positive* |

| Response to Metabolic Acidosis |
|---|
| In response to a metabolic acidosis, a normally functioning renal system is able to secrete additional acid in the form of ammonium $NH_4^+$, generally as NH4Cl.<br>While $NH_4^+$ is an unmeasured urinary cation, its presence in urine can be estimated by using the measurement of urine $Cl^-$ as a proxy since ammonium (a cation) is generally secreted with chloride (an anion) to maintain electroneutrality |

| With a Normally Functioning Renal System | If the Renal System is not functioning normally |
|---|---|
| ***Negative UAG*** | ***Positive UAG*** |
| If the renal system is able to appropriately increase the secretion of ammonium in response to a metabolic acidosis, the amount of $NH_4Cl$ in the urine increases and the UAG or net charge will be negative:<br><br>(urine $Na^+$ + urine $K^+$) – (a larger amount of urine Cl-)= a negative number.<br><br>***A negative UAG*** *suggests that renal tubular dysfunction is not the cause of the metabolic acidosis.*<br>***This may be seen in Gastrointestinal causes of metabolic acidosis such as diarrhea*** | If, the renal system is not able to appropriately increase the secretion of ammonium in response to the metabolic acidosis, the amount of NH4Cl in the urine remains unchanged or even decreases, and the UAG or net charge will be positive:<br><br>(urine $Na^+$ + urine $K^+$)- (a smaller amount of urine $Cl^-$) = a positive number<br><br>***A positive UAG*** *suggests that there is impaired renal acid secretion and that the renal system is the cause of, or at least contributing to, the metabolic acidosis.*<br>***This may seen in Distal Renal Tubular Acidosis or chronic kidney disease*** |



**172. Answer is D (Distal Renal Tubule defect):** *Harrison's 18th/Chapter 284*

*Dent's Disease is a defect of the Proximal Renal Tubules (and Not Distal Renal Tubules).*

*Dent's disease is a rare X-linked proximal renal tubulopathy characterized by Low Molecular Weight proteinuria associated with hypercalciuria, which may provoke nephrolithiasis, nephrocalcinosis and renal failure. Dent disease is typically caused by a defect in the chloride channels of the* ***proximal renal tubule*** *(Most common genetic abnormality is a mutations of ClC-5, a member of the family of voltage-gated CLC chloride channels expressed in cells lining the proximal tubule of the kidney). Since Dent's Disease is an X-Linked disorder, males are typically more often affected than women.*

*Lowe Syndrome and Dent's Disease are X Linked hereditary disorders caused by a defect in the proximal tubule function that result in partial or complete Renal Fanconi syndrome (Type 2 RTA)*

## Disorders of Renal Vasculature

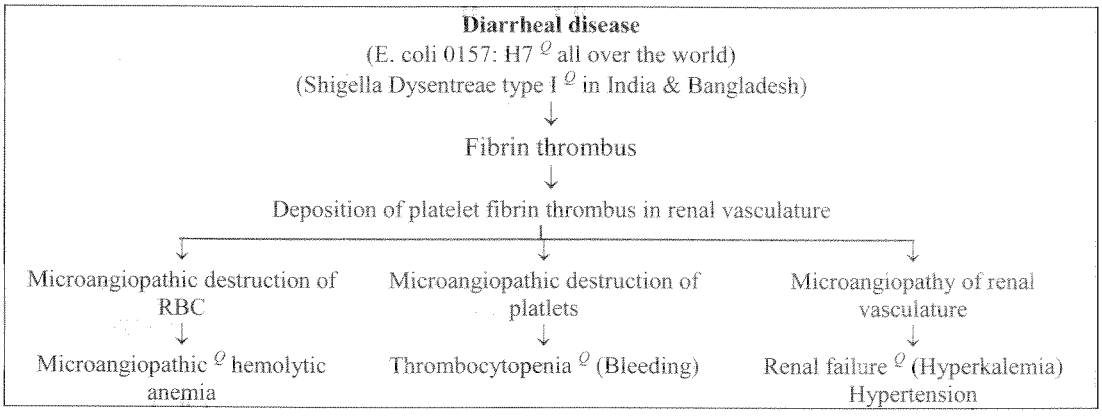
### HUS

**173. Answer is A (HUS):** *CMDT 2005 / 504*

*The child in question presents with thrombocytopenia and evidence of renal failure following a diarrheal disease. This suggests a diagnosis of HUS.*

| HUS should be strongly suspected in any child, who presents with: |
|---|
| • Anemia, Q<br>• Bleeding Q (which is due to thrombocytopenia), Q or<br>• Renal failure Q (as indicated here by decreased urine output) Q |
| Specially so, if it occurs after a diarrheal illness Q<br>(due to infection with E. coli, Shigella or Salmonella) Q. |

**HUS** - It is a vessel wall disorder charactarized by deposition of localized platelet and thrombi within the renal vasculature




**174. Answer is D (Serotoxin has no role in pathogenesis):** *Hoffman's Hematology (2009)/2106; Wintrobe's Hematology 12th/1319, 1320; Harrison's 18th/970; CPDT 20th/685; Chronic Complex Disease of Childhood (Universal Publishers) 2011/365*

***Serotoxins also known as Shiga like toxin (SLT; STx) or Verotoxin (VT) are the most commonly implicated toxins in the pathogenesis of Hemolytic Uremic Syndrome.***

**Serotoxin/Shiga Like Toxin/ShigellaVerotoxin (VT) is the most common toxin implicated in the pathogenesis of HUS**

Typical Hemolytic Uremic Syndrome is a diarrhea-associated condition triggered by intestinal infection with *serotoxin/shiga like toxin producing bacteria*

- *ShigellaDysentreas type I, producing Shiga Toxin is the most common organism in India & Bangladesh*
- *Shiga like toxin (serotoxin) producing E. coli (EHEC 0157:H7) is the most common implicated agent worldwide.*

**Hemolytic Uremic syndrome usually follows Haemorrhagic Colitis**

*Typical Hemolytic Uremic syndrome is diarrheal associated disease* triggered by intestinal infection with Shiga toxin or Shiga like toxin producing bacteria (This is termed as D (+) HUS).

***These cases of HUS are typically preceded by episodes of bloody diarrhea or Haemorrhagic colitis***

(Most common presenting features)

| **Typical** HUS; D (+) HUS | Atypical HUS; D (-) HUS |
|---|---|
| • *Shiga producing toxin is implicated in pathogenesis*<br>• *Usually preceded or associated with bloody diarrhea (Hemorrhagic colitis)* | • *Shiga producing toxin is not implicated in pathogenesis*<br>• *Neither preceded nor associated with bloody diarrhea* |

**Fever in Hemolytic Uremic Syndrome is usually mild or absent**

*'Fever is typically mild or absent' – Hoffman's Hematology (2009)/2106*

*'HUS often presents without fever or neurological dysfunction'*

*– Washington Manual of Hematology and Oncology Subspecialty Consult (2003)/53*

| PENTAD of Thrombotic Microangiopathy | TTP (Pentad) | HUS (Triad) |
|---|---|---|
| *Microangiopathic Hemolytic Anemia* | +++ | +++ |
| *Thrombocytopenia* | +++ | +++ |
| *Renal Dysfunction* | +++ | +++ *(Predominates)* |
| ***Fever*** | +++ | ***+/- (Uncommon)*** |
| *Neurological Dysfunction* | +++ | *+/- (Uncommon)* |

**Hemolytic Uremic Syndrome is often a self-limiting condition**

*'**Typical HUS (D+ HUS) is often a self limiting condition**, although many children need extensive supportive care including dialysis, for a period of time' – 'Chronic Complex Diseases of Childhood' (Universal Publishers) 2011/363*

- ***The treatment of typical HUS (D+ HUS) is essentially supportive.***
- *No specific treatment is available.*
- *Plasmapharesis (Plasma therapy) is of little or no value (as opposed to TTP)*
- *Extensive supportive care including dialysis forms the mainstay of management*
- ***Most commonly children recover from the acute episode in 2-3 weeks (CPDT)***
- *Children with HUS may develop chronic residual renal disease or hypertension later in life and hence follow up of patients with HUS should include serial monitoring of renal function and blood pressure.*

**175. Answer is D (Neuropsychiatric manifestations):** *CMDT 2005 / 504*

***Absence of neurological manifestations has been termed as a chracteristic essential diagnoistic feature for HUS in CMDT text.** Hyperkalemia is a manifestation of Renal failure and hence appears justified.*

**Essentials of diagnosis as mentioned in CMDT:**

- Microangiopathic hemolytic anemia
- Thrombocytopenia
- Renal failure
- Elevated serum LDH
- Normal coagulation tests
- *Absence of Neurological abnormality*

*There are no neurological manifestations other than those due to uraemia – CMDT*
*Neurological symptoms other than those associated with uremia are uncommon – Harrison*
*Nevertheless, confusion does prevail as Nelson confuses the issue – Extra renal manifestations may include CNS manifestations – Nelson*

**176. Answer is D (Positive coomb's test):** *CMDT 2005 /504; Nelson 16th/1587*

*Coomb's test is negative in HUS*

**Laboratory findings in HUS** – *CMDT 2002 / 556*

1. Anemia: Microangiopathic hemolytic
   Red blood cell fragmentation on peripheral smear
   Helmet cells / Burr cells
2. Thrombocytopenia
3. WBC counts rise (Nelson 16th/ 1587)
4. LDH levels are elevated out of proportion to degree of hemolysis
5. *Coomb's test is negative*
6. Tests of coagulation are normal (exclude DIC) with the exception of – elevated fibrin degradation products (explains hypofibrinogenemia)

**177. Answer is A (Hemolytic uremic syndrome):** *Harrisons 15th/ 750; Harrison 17th/723 Harrison 18th/p 970*

***Patient presents with Renal failure 5 days after an episode of diarrhea. He has associated Anemia and Thrombocytopenia and thus qualifies the triad of HUS i.e.***

- Anemia
- Thrombocytopenia
- Renal failure

***Remember***

- *In contrast to TTP, the **HUS** remains localized to the kidney, where hdyaline thrombi are seen in the afferent arterioles and glomerular capillaries. Such thrombi are not present in other vessels and **neurologic symptoms, other than those associated with uremia are uncommon**.*
- DIC is not seen in both TTP & HUS

## Benign /Malignant Hypertension

**178. Answer is D (Hyaline Arteriosclerosis) :** *Robbins 7th /1006, 1007, 1008, Harsh Mohan 5th/ 711, 712, 713*

***Hyaline arteriosclerosis is a feature of Benign Nephrosclerosis associated with benign phase of Hypertension. It is not a feature of Malignant Hypertension.***

| *Benign Nephrosclerosis* | *Malignant Nephrosclerosis* |
|---|---|
| *This term is used to describe the changes in kidney associated with benign phase of hypertension* | *This term is used to describe the changes in kidney associated with malignant or accelerated hypertension* |
| *Gross* | *Gross* |
| • Kidney *size is either* normal[Q] *or may be moderately* reduced[Q] | • Kidney size *is* variable[Q] *May be* smaller in size[Q] *(when superimposed on benign nephrosclerosis) or Larger in* size *(enlarged)[Q] than normal (patients who develop malignant hypertension in pure form)* |
| • Grain leather appearance[Q] *: The cortical surface has a fine even granularity* | • Flea bitten appearance[Q]: ***The cortical surface** may show multiple small **peticheal haemorrhages**[Q] from rupture of arterioles or glomerular capillaries.* |
| *Microscopic (Vascular Changes & Parenchymal Changes)* | *Microscopic (Vascular Changes & Parenchymal Changes)* |
| • **Hyaline Arteriosclerosis** [Q] *Narrowing of the lumens of arterioles and small arteries caused by thickenning and hyalnization of the walls* | • **Fibrinoid necrosis of arterioles**[Q] **(Necrotizing arteriolitis**[Q]**)** *The vessel wall shows fibrinoid necrosis. Represents an acute event and necrosis is usually not accompanied by intense inflammation* |
| • Fibroelastic Hyperplasia[Q]*: in the intima (intimal thickenning[Q]), duplication of elastic lamina and hypertrophy of the 'media'* | • **Hyperplastic intimal sclerosis**[Q] / Onion – Skinning[Q] **Concentric laminae** *of proliferated smooth muscle cells, collagen and basement membrane* **(producing intimal thickenning)** |
| • *Parenchymal changes (due to ischaemic) Variable degree of Atrophy of parenchyma due to ischaemia* | • *Parenchymal changes (due to ischaemia) Variable degree of atrophy of paranchyma due to ischaemia. Infarction necrosis distal to abnormal vessels may be seen* |

**179. Answer is C (Hyaline Arteriosclerosis) :** *Robbins 7th / 1006, 1007, 1008, Harsh mohan 5th / 711, 712, 713*

***The charachteristic histological finding in Benign Hypertension is Hyaline arteriosclerosis***

| *Benign Nephrosclerosis* | *Malignant Nephrosclerosis* |
|---|---|
| *This term is used to describe the changes in kidney associated with benign phase of hypertension* | *This term is used to describe the changes in kidney associated with malignant or accelerated hypertension* |
| *Gross* | *Gross* |
| • Kidney *size is either* normal[Q] *or may be moderately* reduced[Q] | • *Kidney size is variable*[Q] May be smaller in size[Q] (when superimposed on benign nephrosclerosis) or Larger in size (enlarged)[Q] than normal (patients who develop malignant hypertension in pure form) |
| • Grain leather appearance[Q] *: The cortical surface has a fine even granularity* | • *Flea bitten appearance*[Q]: **The cortical surface** may show multiple small **peticheal haemorrhages**[Q] from rupture of arterioles or glomerular capillaries. |
| *Microscopic (Vascular Changes & Parenchymal Changes)* | *Microscopic (Vascular Changes & Parenchymal Changes)* |
| • **Hyaline Arteriosclerosis** [Q] • *Narrowing of the lumens of arterioles and small arteries caused by thickenning and hyalnization of the walls* | • **Fibrinoid necrosis of arterioles**[Q] **(Necrotizing arteriolitis**[Q]**)** *The vessel wall shows fibrinoid necrosis. Represents an acute event and necrosis is usually not accompanied by intense inflammation* |
| • Fibroelastic Hyperplasia[Q]*: in the intima (intimal thickenning[Q]), duplication of elastic lamina and hypertrophy of the 'media'* | • **Hyperplastic intimal sclerosis**[Q] / Onion – Skinning[Q] **Concentric laminae** *of proliferated smooth muscle cells, collagen and basement membrane* **(producing intimal thickenning)** |
| • *Parenchymal changes (due to ischaemic) Variable degree of Atrophy of parenchyma due to ischaemia* | • *Parenchymal changes (due to ischaemia) Variable degree of atrophy of paranchyma due to ischaemia. Infarction necrosis distal to abnormal vessels may be seen* |

**180. Answer is B (Fibrinoid necrosis):** *Refer previous question*

***Malignant hypertension is characterized by Fibrinoid necrosis** (Necrotizing arteriolitis[Q]) **of arterioles.***

**181. Answer is C (Hyaline Arteriosclerosis):** *Robbins 7th /1006-1008, Harsh Mohan 5th/ 711, 712, 713; Refer previous question*

*Benign hypertension is characterized by hyaline arteriosclerosis.*

## Renovascular Hypertension

**182. Answer is A (Benign Nephrosclerosis):** *Diseases of the Kidney and Urinary Tract (Lippincott Williams & Wilkins) 8th/ 1389; Paediatric Nephrology (Lippincott Williams & Wilkins, 2004)/ 889*

***Benign nephrosclerosis is usually not accompanied by increased production of renin or activation of the renin-angiotensin-aldosterone pathway.***

**Hypertension and Benign vs. Malignant Nephrosclerosis**

*Nephrosclerosis refers to the ischemic changes of the kidney arising from vascular diseases affecting the renal arteries, typically hypertension.* Benign Nephrosclerosis represents a typical change in renal blood vessels as a consequence of chronic nonspecific hypertension. Pathological changes in Benign Nephrosclerosis are usually not significant enough to activate the Renin Angiotensin Pathway. Malignant nephrosclerosis is a more severe form of nephrosclerosis with unique lesions in the form of fibrinoid necrosis of the afferent arterioles that ***can lead to renal ischemia. This activates the renin angiotensin pathway*** which in turn raises the blood pressure even more. Activation of the renin-angiotensin system could be a critical step in the transition from benign to malignant nephrosclerosis. Malignant nephrosclerosis is accompanied by increased production of renin, angiotensin, and aldosterone

**Hypertension in Haemolytic Uremic Syndrome is often renin mediated (Increased Renin)**

*Hypertension in the acute phase of HUS is usually volume related while in the later stages it is often produced as a result of increased renin levels*

**Juxtaglomerular Cell Tumours are associated with high renin levels**

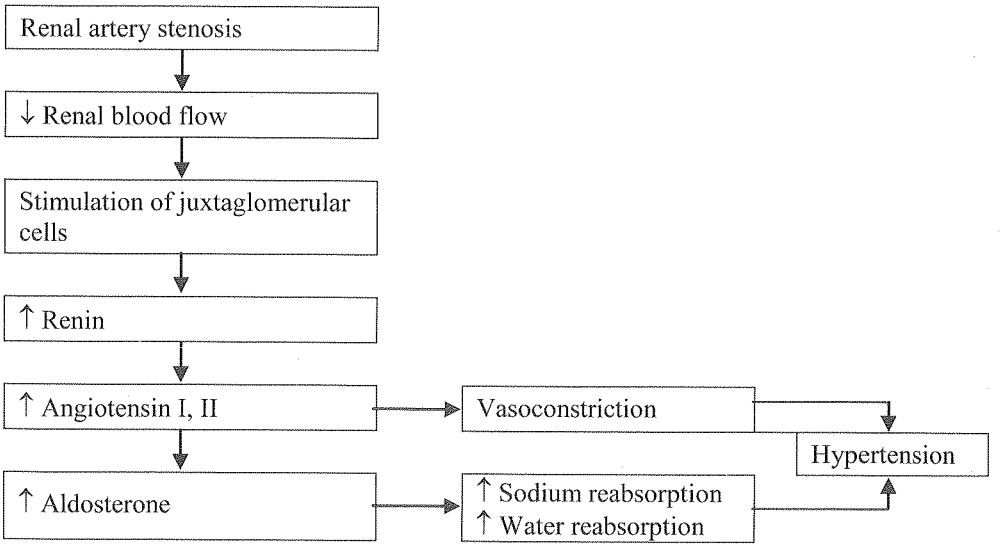
Juxtaglomerular cell tumours may produce excess renin directly and cause hypertension without affecting renal circulation.

**183. Answer is C (Renovascular Hypertension):** *Manual of Endocrinology and Metabolism (Lippincott Williams & Wilkins) 4th/ 184*

***Renovascular Hypertension is associated with High Renin levels (High Renin Hypertension)***
*Essential Hypertension, Conn's Syndrome and Liddle's Syndrome are all associated with Low Renin Hypertension.*

| *Hypertension* | *Renin* | *Aldosterone* |
|---|---|---|
| *Essential Hypertension* | *Low* | *Normal* |
| *Conn's Syndrome* | *Low* | *High* |
| *Liddle's Syndrome* | *Low* | *Low* |
| *Renal Artery Stenosis (Renovascular Hypertension)* | *High* | *High* |

**Renovascular Hypertension is associated with High Renin and High Aldosterone Levels**



**Liddle Syndrome is associated with Low Renin and Low Aldosterone levels**

Liddle's syndrome is an autosomal dominant condition caused by mutations in the genes that encode the β and γ subunits of the mineralocorticoid-dependent epithelial sodium channel. This results in continuous (constitutive) activation of the channel, even in the absence of mineralocorticoid. Clinically, the condition is characterised by early-onset hypertension, with hypokalemia and low levels of rennin and aldosterone. The condition responds to treatment with the potassium-sparing diuretic Amiloride (or triamterene).

**184. Answer is C (Renovascular Hypertension):** *Manual of Endocrinology and Metabolism (Lippincott Williams & Wilkins) 4th/ 184*

***Renovascular Hypertension is associated with High Renin levels (High Renin Hypertension).***

| *Low-renin hypertension* | *High-renin hypertension* |
|---|---|
| • *Congenital Adrenal Hyperplasia*<br>*11β-Hydroxylase deficiency*<br>*17α-Hydroxylase/17,20-lyase deficiency*<br>• *Primary aldosteronism*<br>• *Glucocorticoid-remediable aldosteronism (Dexamethasone-suppressible Hyperaldosteronism)*<br>• *Apparent mineralocorticoid excess (11 β-hydroxysteroid dehydrogenase 2 deficiency)*<br>• *Liddle's syndrome*<br>• *Cushing syndrome* | • *Renovascular abnormalities*<br>• *Juxtaglomerular cell tumors*<br>• *Bilateral endocrine dysfunction of the kidney* |

*Note: Some patients with Cushing's syndrome may have increased plasma renin and renin substrate.*

**185. Answer is B (CT Angiography):** *Harrison 16th/1470; Braunwald 8th/1040; The Cleveland Clinic Cardiology Board Review (Lippincott Williams) 1st/514*

***Spiral CT scan with intravenous contrast (CT angiography) is the most sensitive and specific test amongst the options provided.***

Note:
*Magnetic Resonance Angiography (MRA) has now emerged as the diagnostic test of choice at several centres with a sensitivity and specificity similar or even better than CT Angiography.*
*However as MRA has not been provided amongst the options, CT Angiography remains the single best answer of choice.*
*MRA is also more likely to be used more widely* ***(preferred)*** *because it reduces the possibility of contrast induced nephrotoxicity and avoids exposure to ionizing radiations.*

**Renovascular Hypertension**

| Screening Test of Choice | Gold Standard Diagnostic Test |
|---|---|
| Magnetic Resonance Angiography (MRA)<br>Spiral CT or Angiography (CTA) | Renal Angiography / Arteriography (conventional) |

***MRA is now emerging as the screening test of choice***

**186. Answer is A (Magnetic Resonance Angiography (MRA):** *'The Clevland Clinic Board Review' (Lippincott Williams) 1st/514; Harrison 16th/1470; Cardiovascular Therapeutic 3rd*

***Magnetic Resonance Angiography (MRA) has now emerged as the most sensitive and specific screening test for Renovascular hypertension.***

Note:

*Harrison 16th edition (old) mentions Spiral CT scan as the most sensitive and specific screening test for Renovascular Hypertension, however most recent textbooks now prefer MRA as the screening test of choice with similar or even better sensitivity and specificity than spiral CT Angiography.*

Renovascular Hypertension

**Screening Test**

| Test | Sensitivity (%) | Specificity (%) |
|---|---|---|
| Magnetic resonance angiography (MRA) | 100 | 96 |
| Spiral computerized tomography | 98 | 94 |
| Captopril renogram | 70-93 | 95 |
| Duplex Doppler ultrasonography | 69-96 | 86-90 |
| IVP | ~75 | ~85 |

**Gold Standard / Diagnostic Test**

| Test | Sensitivity | Specificity |
|---|---|---|
| Conventional Renal Angiography | >99% | >99% |

**187. Answer is B (Non specific aorto-arteritis):** *Disease of kidney and urinary tract 8th/1279; Tropical Neurology 1st (2003)/440; Surgical Neuroangigraphy 2nd/115*

***The most common cause of renal artery stenosis in young adults in India is Non specific aorto-arteritis.***

Most common cause of Renovascular Hypertension

- **Elderly patients**: Atherosclerosis
- **Young patients**
  - **India**
    - Non specific Aorto-Arteritis (According to older editions)
    - Takayasu arteritis (According to latest editions)
  - **Western World**: Fibromuscular dysplasia

*The non specific aorto-arteritis causing renal artery stenosis is now believed to be Aorto-arteritis secondary to Takayasu arteritis*

**Aorto-arteritis/Takayasu arteritis is the most common cause of renovascular hypertension in India**

*Non specific Aorto-arteritis is the most common cause of renovascular hypertension in India and China – Tropical Neurology 1st (2003)/440*

*Takayasu arteritis (Aorto-arteritis) is the most common cause of renovascular hypertension in India and China.' – Diseases of kidney and Urinary Tract 8th/1279*

*In India, China, Korea, Japan and other South East Asian countries, Takayasu arteritis is the most common cause of renovaascular hypertension.' – Surgical Neuroangiography 2nd/115*

Note:

*The non specific aorto-arteritis causing renal artery stenosis is now believed to be Aorto-arteritis secondary to Takayasu arteritis*

**188. Answer is D (Polyarteritis nodosa):** *Harrison 16th/1707,2007,2009; CMDT'09/810; API 8th.541; References alongside explanation*

***Amongst the options provided renal artery stenosis is least likely to be seen in association with Polyarteritis nodosa.***

- **Atherosclerosis and Fibromuscular disease**
  - Renal artery stenosis is produced predominantly by atherosclerotic occlusive disease (80% to 90% of patients) or fibromuscular dysplasia (10-15% of patients).- *CMDT'09 p 810*
  - The common cause of renal artery stenosis ***in the middle aged and elderly*** is an atheromatous plaque at origin of renal artery. *Harrison*
  - ***In younger women*** stenosis is due to intrinsic structural abnormalities of the arterial wall caused by a heterogenous group of lesions called 'fibromuscular dysplasia'. - *Harrison 16th/1707*

- **PAN or Takayasu arteritis ?**

*Harrison, CMDT* do not mention PAN or Takayasu arteritis as a cause for renal artery stenosis.
However, Takayasu arteritis is certainly a more common cause of renal artery stenosis than PAN.
Takayasu arteritis (Aorto-arteritis) *is beleiveds to be the most common of renovascular hypertension in India and China. – Diseases of Kidney and Urinary Tract 8th/1279*

**A number of research publications, however show Takayasu arteritis as a cause for renal artery stenosis.**

| Takayasu Arteritis | PAN |
|---|---|
| *Takayasu arteritis (Aorto-arteritis) is the most common cause of renovascular hypertension in India and China.' – Diseases of kidney and Urinary Tract 8th/1279* | Renal artery stenosis in a Case of PAN has only been described as an unusual association and published as a rare case report (single case)<br>***Reference :*** "PAN with renal Artery Stenosis": Indian Pediatrics Volume 41-Jan.17, 2004. |

PAN

Although renal involvement is seen in upto 60% of patients with PAN its pathology does not involve renal artery stenosis.
The pathology involves arteritis without glomerulonephritis and is characterised by aneurysms of small and medium sized arteries. **Stenosis of main renal artery is an unusual association'.**

*-Research paper, www. Indian paediatrics. net/Jan 2004/86.pdf*

**Causes of Renal artery stenosis :** *API 8th/541; Renal Artery Stenosis : Diagnosis and Management - IHJ : May-June 2002, Vol. 54/No. 3*

1. Atherosclerosis
2. Fibromuscular dysplasia
3. Non specific Aorto arteritis
4. Takayasu arteritis and giant cell arteritis (Takayasu > Giant cell)
5. Antiphospholipid syndrome
6. Transplant renal artery stenosis
7. Renal artery embolism
8. Dissecting aneurysm of aorta
9. Radiation arteritis

**189. Answer is C (Condition is nearly always bilateral):** *Harrison 18th/p 2375, 2376 Harrisons 17th/- 1811-1812*

*Presence of hypertension (BP = 160 / 110) and bruit in bilateral flanks suggest a diagnosis of Bilateral Renal Artery Stenosis in this patient.* ***Renal Artery Stenosis is bilateral in 50% of cases and is not nearly always bilateral***

**ACE inhibitors (eg Enalapril) may deteriorate renal function in patients with Bilateral Renal Artery Stenosis**
*ACE inhibitors (eg Enalapril)* are the agents of choice for treatment of hypertension in patients with unilateral renal artery stenosis, but *are* ***contraindicated in patients with bilateral disease***. The presence of bruit in both flanks suggest *bilateral disease in this patient and hence enalapril should not be used*

**Contrast Enhanced Arteriography (Angiography) is the most definitive diagnostic procedure for the diagnosis of Renal Artery stenosis** while Magnetic Resonance Angiography (MRA) is the most sensitive and specific non invasive test (screening test) for its diagnosis.

**Fibromuscular dysplasia is the most common cause of Renal Artery stenosis in young women** while Atherosclerotic disease is the most common cause in middle aged/ elderly patients. *The patient in question is a young female (20 years) and hence the most likely cause of Renal Artery stenosis in this patient is fibromuscular dysplasia*

**Surgical Intervention may be required in patients with Bilateral Renal Artery Stenosis**
*Surgical intervention* in the form of angioplasty and stent placement is indicated when medical therapy has failed to control BP or resulted in > 30% increase in serum creatinine.

**Renal Artery Stenosis: Review**

- Renal Artery stenosis is an important cause of Renovascular Hypertension
- ***Bilateral involvement is seen in half of the affected cases (50%)***

**Etiology**

- Atherosclerotic disease : This is the most common cause in middle aged /elderly patients
- Fibromuscular Dysplasia : ***This is the most important cause in young females***

**Presentation**

- Hypertension
  - Abrupt onset of hypertension
  - Acceleration of previously well controlled hypertension
  - Refractory Hypertension
- Features of increased sympathetic neural activity (which is associated with Renovascular disease)
  - Flushing
  - Loss of nocturnal BP decrease
  - Putonomic instability
  - Rapid BP swings
- Progressive Renal failure / Azotemia

**Diagnosis**

| Magnetic Resonance Angiography (MRA) | Contrast Enhanced Arteriography |
|---|---|
| MRA is the most sensitive (>90%) and specific (95%) non invasive test for the diagnosis of RAS | Contrast enhanced angiography is the most definitive (but invasive) diagnostic procedure for diagnosis of RAS |

**Management**

**Medical Therapy with ACE Inhibitors or Angiotensin Receptor Blockers**

| Indications | Contra indications |
|---|---|
| **Unilateral Renal artery Stenosis**<br>- With hypertension & normal renal function (more effective than other antihypertensives)<br>- With hypertension & abnormal renal function (beneficial effect on survival without affecting renal function)<br>- With hypertension, diabetes, proteinuria and normal or abnormal renal function (effective antihypertensives) | **Bilateral Renal Artery stenosis**<br>ACE inhibitors or Angiotensin receptor blockers are contraindicated in patients with Bilateral renal artery stenosis or stenosis in a solitary kidney as their use in such patients leads to worsening of renal failure<br>(These patients are especially sensitive to decline in intraglomerular pressure) |

**Note**

***Acute Renal Failure / Worsening of Renal Failure with Angiotension Receptor Inhibitors is a diagnostic clue to the diagnosis of renal artery stenosis (indicates bilateral disease)***

**Surgical Therapy with Angioplasty + Stent placement**

*Should be considered only after optimal medical therapy has failed to achieve goal BP or resulted in a > 30% increase in serum creatinine*

## Renal Vein Thrombosis

**190. Answer is B (Membranous Glomerulopathy):** *Thrombosis Hemorrhage 3rd/724; Harrison 14th/ 1559; 16th/1684; 17th/1790 Harrison 18th/p 2345*

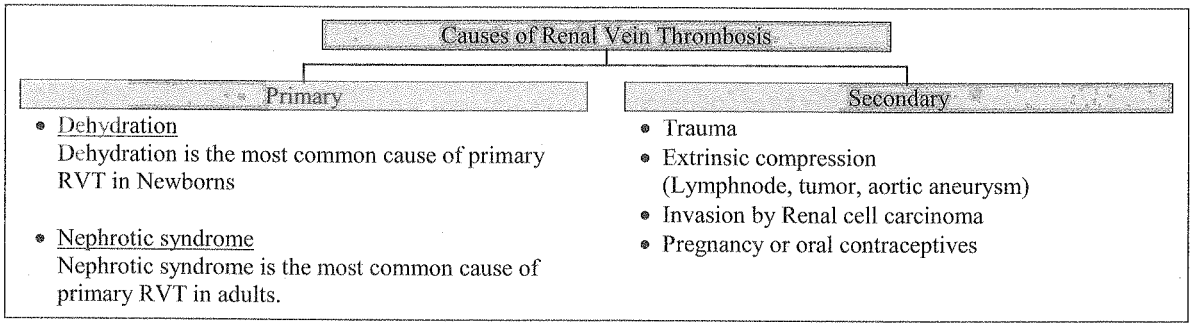
***Membranous glomerulonephritis has the strongest association with development of thrombisis in Renal veins.***
*- Thrombosis & Hemorrhage 3rd/724*

*Nephrotic Syndrome accompanying membranous glomerulopathy and certain carcinomas predisposes to Development of Renal vein thrombosis (which occurs in 10-50% of patients with these disorders)-Harrison*

**Nephrotic Syndrome: Common Renal pathologies causing Renal Vein Thrombosis**

- *Membranous Glomerulonephritis (strongest association)*
- *Membranoproliferative Glomerulonephritis*
- *Amyloidosis*
- *Lupus Nephritis (Thrombosis & hemorrhage 3rd/724)*

*Nephrotic syndrome due to diabetic mellitus, minimal change disease and focal segmental sclerosis are rarely associated with renal vein thrombosis*




**191. Answer is A,B,C,D,E (All of the above)** : *Harrison 18th/p 2382 Harrison 17th/1815*

***Trauma, Renal Cell Ca, Pregnancy, Nephrotic Syndrome and Dehydration can all be associated with Renal Vein Thrombosis***

| **Conditions associated with Renal Vein Thrombosis** : *Harrison 17th/1815* |
|---|
| *Trauma* |
| *Extrinsic compression (lymph nodes, aortic aneurysm, tumor)* |
| *Invasion by renal cell carcinoma* |
| *Dehydration (infants)* |
| *Nephrotic syndrome* |
| *Pregnancy or oral contraceptives* |

**192. Answer is B (Membranous Glomerulopathy):** *Harrison 16th /1684; 15th /1584 - 85; Harrison 14th / 1559; Thrombosis and Hemorrhage 3rd/724*

***Renal vein thrombosis is most commonly associated with nephrotic syndrome secondary to membranous glomerulopathy.***

*'Amongst kidney pathologies causing nephritic syndrome, membranous glomerulopathy has the strongest association with the development of thrombosis in the Renal vein. – Thrombosis & Hemorrhage 3rd/724*

*'Nephrotic Syndrome accompanying **membranous glomerulopathy** and certain carcinomas predisposes to development of Renal vein thrombosis (which occurs in 10-50 % of patients with these disorders)' - Harrison*

**193. Answer is E (PSGN):** *Harrison 16th/1684, 1707; Thrombosis & Hemorrhage 3rd/724*

***Post streptococcal Glomerulonephritis has not been mentioned as a cause of Renal Vein thrombosis***

Nephrotic Syndrome: Common Renal pathologies causing Renal Vein Thrombosis

- *Membranous Glomerulonephritis (strongest association)*
- *Membranoproliferative Glomerulonephritis*
- *Amyloidosis*
- *Lupus Nephritis (Thrombosis & hemorrhage 3rd/724)*

*Nephrotic syndrome due to diabetic mellitus, minimal change disease and focal segmental sclerosis are rarely associated with renal vein thrombosis*

**194. Answer is D (Renal vein thrombosis):** *Nelson 16th/ 1589*

***Although presentation of patient is similar to that of hemolytic uremic syndrome the presence of marked enlargement of both kidneys takes the whole diagnosis in favour of renal vein thrombosis.***

**Note :** *Nelson 16th – 1587 :*

| ***Patients who have bilateral renal vein thrombosis may be difficult to distinguish from those with the hemolytic uraemic syndrome.*** |
|---|
| - Both disorders may be preceded by gastroenteritis and in both children may present with dehydration, pallor and evidence of microangiopathic hemolytic anemia, thrombocytopenia and acute renal failure.<br>- The marked enlargement of kidneys of a child with renal vein thrombosis helps to distinguish the disorder.<br>- Doppler flow study or angiography of IVC may be necessary to confirm the diagnosis. |

*Patient in question has marked enlargement of both kidneys which takes the whole diagnosis in favour of renal vein thrombosis.*

## Nephrolithiasis and Nephrocalcinosis

### Nephrolithiasis (Renal/Ureteric Stones)

**195. Answer is D (Uric acid stones are resistant to ESWL):** *Schwartz 8th/1547; Bailey 24th/1319; Clinical Pediatric Urology 4th/1238*

*Uric acid stones are not resistant to ESWL.*

*Uric acid stones are infact most responsive to Lithotripsy along with calcium oxalate dehydrate stones.*

| Stone Type | X Ray finding | Predisposing features | Comments |
|---|---|---|---|
| **Oxalate stones** (calcium oxalates) | ***Radiopaque*** | *Hypercalciuria*<br>*Hyperoxaluria* | *Most common types of Renal Calculi* |
| **Phosphate Stones**<br>- *Calcium phosphate*<br>- *Magnesium Ammonium Phosphate (Struvite)* | *Radiopaque* | • ***Excess Alkali consumption***<br>• ***Alkaline urine***<br>• *Infection with urease splitting organisms eg. Proteus* | *Struvite stones are often solitary*<br>*Struvite stones form staghorn calculi* |
| **Cystine Stones** | *Radiopaque* | *Inherited cystinuria* | • ***Form in acidic urine***$^{Q}$<br>• *Extremely hard stones*$^{Q}$<br>• *Relatively resistant*$^{Q}$ *to fragmentation with E5WL* |
| **Uric acid stones** | *Radioluscent* | *Gout*<br>*Hyperuricemia* | • *Form in acidic urine*<br>• ***Most responsive to lithotripsy*** |
| **Xanthine stones** | *Radioluscent* | *Deficiency of xanthine oxidase* | - |

**196. Answer is C (Cystine stones):** *Schwartz 8th/1547; Bailey & Love 24th/1319; Clinical Pediatric Urology 4th/1238; Washington Manual of Ambulatory Therapeutics 1st (2002)/449*

*Cystine stones are most resiatnt to Lithotripsy.*

**Lithotripsy and Renal Calculi Composition**

| Composition most responsive to Lithotripsy | Composition Relatively resistant to Lithotripsy (Moderate Responsive) | Composition most Resistant to Lithotrispsy |
|---|---|---|
| *Uric acid calculi*<br>*Calcium oxalate Dihydrate* | *Struvite (Phosphate)*<br>*(Calcium oxalate Monohydrate)* | ***Cystine Calculi***<br>*(Calcium oxalate Monohydrate)* |

**197. Answer is A (Calcium Oxalate Monohydrate):** *Smith's textbook of Endourology 1st (2007)/143*

***Calcium Oxalate Monohydrate Stones (and cysteine) stones are very hard to break by ESWL.***

*'Very hard stones such as cysteine or calcium oxalate monohydrate are more likely to fail ESWL'.*

*— Smith's Textbook of Endourology 1st/143*

*'Likelihood of fragmentation with ESWL depends on stone composition. Less effective for stones composed of cystine or calcium oxalate monohydrate (very hard)' – Oxford handbook of urology (2005)/366*

*'Softer stones (calcium oxalate dehydrate, uric acid, apatite, and struvite) are more easily fragmented with SWL than are harder stones (calcium oxalate monohydrate, brushite, and cystine) - Therapy in Nephrology & Hypertension (Sanders) 2nd/406*

**198. Answer is B (Uric Acid):** *Bailey and Love 24th/1317; Smith's Urology 16th/262; 'Beat the Boards' 1st (2006)/214*

*Uric acid stones are characteristically Radiolucent*

**Renal Stones**

| Radiopaque | | Radioluscent |
|---|---|---|
| • *Oxalate Stones*<br>- *Calcium Oxalate*<br>• *Phosphate Stones*<br>- *Calcium phosphate*<br>- *Magnesium ammonium phosphate (struvite)*<br>• *Cystine stones* | | • *Uric Acid Calculi*<br>• *Xanthine Calculi*<br>• *Indinavir Calculi (complication of Indinavir use-Proteinase inhibitor)*<br>• *Triametrene calculi (complication of Triamterene use-Antihypertensive)* |

**199. Answer is B (Triple phosphate):** *Bailey 24th/1316. 1319; Smith's Urology 16th/262; Schwartz 8th/1547; Clinical Pediatric Urology 4th/1238*

***Phosphate stones (Triple phosphate stones) form in the presence of high concentration of ammonia which essentially means that they form when the urine is infected (UTI) with Urea splitting organisms (eg. Proteus, Kleibsella, Pseudomonas sp.)***

Triple Phosphate Stones (Phosphate stones)

- *Triple phosphate stones are composed predominantly of magnesium ammonium phosphate (struvite) with variable amounts of calcium phosphate.*
- *They form in the presence of high urinary concentration of ammonia (bicarbonate and carbonate)*
- *They form in cases of UTI when urine is infected with urea splitting bacteria i.e. Proteus, Kleibsella and Pseudomonas*
- *They form in urine with an alkaline pH.*

*Urea splitting organisms split urea to ammonia there by providing an alkaline pH which facilitates precipitation of phosphate crystals.*

| Stone Type | X Ray finding | Predisposing features | Comments |
|---|---|---|---|
| **Oxalate stones** (calcium oxalates) | ***Radiopaque*** | *Hypercalciuria*<br>*Hyperoxaluria* | *Most common types of Renal Calculi* |
| **Phosphate Stones**<br>- *Calcium phosphate*<br>- *Magnesium Ammonium Phosphate (Struvite)* | *Radiopaque* | • ***Excess Alkali consumption***<br>• ***Alkaline urine***<br>• *Infection with urease splitting organisms eg. Proteus* | *Struvite stones are often solitary*<br>*Struvite stones form staghorn calculi* |
| **Cystine Stones** | *Radiopaque* | *Inherited cystinuria* | • ***Form in acidic urine***[Q]<br>• *Extremely hard stones*[Q]<br>• *Relatively resistant*[Q] *to fragmentation with E5WL* |
| **Uric acid stones** | *Radioluscent* | *Gout*<br>*Hyperuricemia* | • *Form in acidic urine*<br>• ***Most responsive to lithotripsy*** |
| **Xanthine stones** | *Radioluscent* | *Deficiency of xanthine oxidase* | - |

**200. Answer is A (Phosphate):** *Bailey 24th/1316; Smith's Urology 16th/262; Beat the Boards 1st (2006)/214*

***Phosphate stones (Triple phosphate stones) form in the presence of high concentration of ammonia which essentially means that they form when the urine is infected (UTI) with Urea splitting organisms (eg. Proteus, Kleibsella, Pseudomonas sp. )***

Triple Phosphate Stones (Phosphate stones)

- *Triple phosphate stones are composed predominantly of magnesium ammonium phosphate (strurite) with variable amounts of calcium phosphate.*
- *They form in the presence of high urinary concentration of ammonia (bicarbonate and carbonate)*
- *They form in cases of UTI when urine is infected with urea splitting bacteria i.e. Proteus, Kleibsella and Pseudomonas*
- *They form in urine with an alkaline pH.*

*Urea splitting organisms split urea to ammonia there by providing an alkaline pH which facilitates precipitation of phosphate crystals.*

**201. Answer is B (Increased peristalsis of the ureter to overcome obstruction)** : *Smiths Urology 17th /31*

*The severity and colicky nature of ureteric colic pain are caused by the hyperperistasis and spasm of smooth muscles of the ureter as it attempts to rid itself of a foreign body or to overcome obstruction – Smith*

Pain from Acute obstruction of Ureter
(Stone or Blood clot)

| Back Pain | Severe Colicky Pain |
|---|---|
| This results from renal capsular distention | This results from renal, pelvic and ureteral muscle spasm. The severity and ***colicky nature of this pain are caused by the hyperperistalsis and spasm of this smooth muscle organ (ureter) as it attempts to rid itself of a foreign body or to overcome obstruction.*** |

**202. Answer is A (At pelvic brim):** *S. Das 4th/408; Bailey & Love, 24th/1317; Smith's Urology 17th/31*

*Pain radiating to medial side of thigh and perineum suggetsts a stone in lower portion of ureter (proximal to orifice) or at pelvic brim.*

Location of Ureteric colic (pain) : Review

Pain classically radiates from costovertebral angle, down towards the lower anterior abdominal quadrant
***In Men*** it may also be felt in the bladder, scrotum or testicles
***In Women*** it may also be felt in the vulva

Location of Ureteric Pain

| Stone in upper ureter | Stone in the midportion of ureter | | Stone in the lower portion of ureter Proximal to orifice | Stone in the intramural portion of ureter At the level of orfice or orfice involved due to edema |
|---|---|---|---|---|
| | Right side | Left side | | |
| Pain radiates to Testicles *(T11,T12)* [*Nerve supply of testicles is similar to that of kidney & upper ureter*] | Pain referred to McBurneys point and *simulates appendicitis (T12, L1)* | Pain referred to left lower quadrant and *simulates diverticulitis*[Q] or other disease of the descending or sigmoid colon *(T12, L1)* | pain is *referred to inner side of thigh or groin (L1, L2)* | Symptoms of vesical irritability such *as frequency and urgency may occur* |

**203. Answer is D (Genitofemoral nerve):** *Gray's Anatomy 38th/18*

*Pain of uerteric colic is refered to the proximal anterior aspect of thigh (groin) via supply of the genitofemoral nerve (L1)*

**204. Answer is D (Ureteroscopic Retrieval) :** *Bailey Love 23rd/1189; Smith's general urology 15th/308, 309*

*The patient in question has a small calculus (1.0 cm) in size, which is located in the distal ureter and hence is amenable to ureteroscopic removal. The presence of proximal hydroureteronephrosis indicates obstruction and forms the indication for stone removal.*

**Indications and methods for removal of stone**

**Indications for stone removal**
- *Repeated attacks of colic*
- *Stone is too large to pass*
- *Stone is enlarging*
- *Stone is not moving*
- *Stone is causing complete obstruction of the kidney*
- *Urine is infected*

| Ureteroscopic Removal | Extracorporal shock wave Lithotripsy | Percutaneous Nephrolithotripsy |
|---|---|---|
| • *Small stone*<br>• *Stone in lower part of ureter within 5-6 cm of ureteric orfice* | • *Best for proximal stones* that can be identified by the imaging system of Lithotriptor<br>• Stones in miduretor can be pushed up in the pelvis and *then* exposed to shock waves<br>• Not appropriate if complete obstruction is present<br>• *Stones < 2.0 to 2.5 cm can be removed* | • It is done for proximal ureteric cacluli<br>• Stones > 2.5 cm, those that are resistant to shock waves |

**Open Surgery** *is done very rarely nowadays when all methods have failed, Urethrolithotomy is done for long standing calculi not accessible by instruments and ESWL.*

**205. Answer is D (ESWL):** *Refer previous question*

*The patient in question has a small calculus (< 2.5 cm) located in the proximal portion of the renal tract (pelvis). Such stones are easily amenable to ESWL which is the management of choice.*

**206. Answer is A (Endoscopic removal):** *Refer previous question*

*Stones in the lower part of ureter within 5-6 cm of ureteric orifice (that are small in size) are best managed by Ureteroscopic (Endoscopic) removal.*

**207. Answer is C (Renal stone):** *Clinical Surgery by S. Das*

*Calcification on the right side of the abdomen on an AP view and calcification overlying the spine on lateral view is consistent with diagnosis of renal stones.*

***Characteristics of a Renal stone that aid in the diagnosis*** :
- *In lateral view the* ***Renal stone lies superimposed on shadow of vertebral column*** *while gall stones are seen well infront of the vertebral bodies.*
- *Renal calculii moves with respiration*[Q] which can be verified with two exposures, one in full inspiration & other in full expiration.
- Density of a Renal stone is uniform, while a gall stone is less dense in the centre.
- *Renal stone take the shape of the Renal pelvis*[Q] & calyces while a solitary *gallstone* is usually round and *multiple ones are multifaceted*[Q].
- *Majority of Renal calculi are Radioopaque*[Q] except *pure uric acid stones* which *are Radiolucent*[Q].

A renal calculus has to be differentiated from
1. Gallstone[Q]
2. Calcified Lymphnode[Q]
3. Calcified costal cartilage[Q]
4. Calcified aneurysm of the abdominal aorta[Q]

**208. Answer is D (Medullary cystic kidney):** *Harrison 18th/p 2382, 2383 Harrisons 17th/1815, 1816; Ultrasound of the Urogenital system' by Baxter (2006) /32, 33*

***Nephrocalcinosis is a fracture of medullary sponge kidney disease but is not a feature of Medullary cystic kidney disease or Nephronophthysis.***

*Distal RTA, Sarcoidosis and Milk Alkali syndrome are established causes for Nephrocalcinosis.*

**Nephrocalcinosis**

Nephrocalcinosis is a broad term that refers to pathological deposition of calcium in the renal parenchyma
Nephrocalcinosis may present as medullary nephrocalcinosis or cortical nephrocalcinosis

Causes of nephrocalcinosis

| **Medullary** (common form of Nephrocalcinosis) | **Cortical** (Uncommon /Unusual with incidence <5%) |
|---|---|
| • Renal tubular acidosis (distal or Type I)<br>• Oxalosis<br>• Papillary necrosis<br>• Medullary sponge kidney<br>• Frusemide abuse<br>• Bartter Syndrome<br>• Hypercalcemia<br>- Primary hyperparathyroidism<br>- Sarcoidosis<br>- Vitamin D excess<br>- Hypercalcemia of malignancy<br>- Cushing disease<br>- Milk-alkali syndrome | *Renal cortical necrosis*<br>*Chronic glomerulo nephritis*<br>*Transplant rejection*<br>*Tuberculosis*<br>*Oxalosis*<br>*Oxalosis typically causes both cortical and medullary nephrocalcinosis* |

**209. Answer is D (Pseudohypoparathyroidism):** *Refer previous question*

***Pseudohypoparathyroidism is not associated with nephrocalcinosis***

*Primary hyperparathyroidism. Medullary Sponge Kidney and Vitamin D excess are established causes for nephrocalcinosis.*

**210. Answer is A & E (Medullary sponge kidney & Hyperparathyroidism):** *Refer previous question*

***Medullary sponge kidney and Hyperparathyroidism are established causes of Nephrocalcinosis.***

**211. Answer is B (*Calcium Restriction*):** *'The Washington Manual Nephrology Subspecialty Consult' 2nd/245*

***Low protein, Low sodium and Normal Calcium diet is recommended for patients with calcium nephrolithiasis***

**Dietry Intervention in patients with Calcium Nephrolithiasis**

*'Dietary intervention plays a cardinal role in the preventive treatment of calcium nephrolithiasis. Studies have shown that a **low protein, low salt diet significantly reduces nephrolithiasis** recurrence rates in patients with idiopathic hypercalciuria. Long term dietary compliance with a low protein, low salt diet has been shown to be superior to a low calcium diet in prevention of nephrolithiasis. **A low calcium diet may increase the intestinal absorption of oxalate reducing the effectiveness of this therapy. Therefore low calcium diets are not recommended.** Diets containing 700 to 800 mg of calcium are adequate for patients with idiopathic hypercalciuria. Low protein diets reduce purine intake, resulting in reduced systemic acid and uric acid loads. Low sodium diets reduce the amount of calcium in urine'*

*- The Washington Manual Nephrology Subspecialty Consult' 2nd/245*

## Congenital Diseases of the Kidney

**212. Answer is B (Autosomal dominant):** *Harrison 14th/ 380; 15th/386; 16th/1694; 17th/1797; Harrison 18th/p 2355 Robbins 7th/962, 963*

***Adult polycystic kidney disease is inherited as autosomal dominant trait -Harrison 16th/1694***

**Remember:**

| Autosomal dominant disorders: | Autosomal recessive disorders: | X-Linked disorders: |
|---|---|---|
| Familial hypercholesterolemia | Deafness | Hemophilia A ♀ (recessive) |
| Hereditary nonpolyposis colon cancer | Albinism ♀ | G6PD deficiency ♀ (recessive) |
| Polyposis of the colon ♀ | Wilson's disease ♀ | Ducchene/Becker muscular dystrophy ♀ (recessive) |
| BRCA1 and BRCA2 breast cancer | Hemochromatosis ♀ | Fabry's disease |
| Hereditary hemorrhagic telengiectasia | Sickle cell anemia ♀ | Ocular albinism |
| Marfan's syndrome ♀ | β thalassemia ♀ | Testicular feminization |
| Hereditary spherocytosis ♀ | Cystic fibrosis ♀ | Chronic granulomatous disease |
| Adult polycystic kidney disease ♀ | Hereditary emphysema | Hypophosphatemic rickets ♀ (dominant) |
| Huntington's chorea ♀ | ($\alpha_1$ antitrypsin deficiency) | Fragile-X syndrome ♀ (recessive) |
| Acute intermittent porphyria ♀ | Homocystinuria ♀ | Color blindness ♀ |
| Osteogenesis imperfecta tarda ♀ | Freidrich's ataxia ♀ | |
| von Willebrand's disease ♀ | Phenylketonuria ♀ | |
| Myotonic dystrophy ♀ | Fanconi's Syndrome -[*H 14th/ 2201*] | |
| Familial hypertrophic cardiomyopathy | Gaucher's Disease - [*H 14th/ 2174*] | |
| Neurofibromatosis ♀ | | |
| Tuberous sclerosis ♀ | | |
| Otospongiosis ♀ | | |
| Achondroplasia ♀ | | |

**213. Answer is B (Chromosome 16 and chromosome 4):** *Harrison's 18th/Chapter 284*

***Autosomal Dominant Polycystic Kidney Disease (ADPKD) is caused by mutations of either the PKD1 gene on chromosome 16 or the PKD2 gene on chromosome 4.***

**Polycystic Kidney Disease is primarily inherited as an autosomal dominant trait (ADPKD)**

| *Autosomal Dominant Polycystic Kidney Disease* |
|---|
| • *Mutations in the PKD-1 gene on **chromosome 16** (ADPKD-1) (85% of cases)* |
| • *Mutations in the PKD-2 gene on **chromosome 4** (ADPKD-2) (Remainder)* |

**214. Answer is B (Hypertension is rare):** *Harrison 15th/1598, 1599; 16th/1694; 17th/1797,1798; Harrison 18th/p 2355, 2356 Robbins 7th /962, 963*

***Hypertension is common in patients with autosomal dominant polycystic kidney disease. It is found in 75% of adults and 20 to 30% of children – Harrison 16th/1694***

**Adult Polycystic kidney:**

| **Inheritance : Autosomal Dominant** | |
|---|---|
| **Pathology:** | |
| - Kidneys are grossly enlarged with multiple cysts<br>- Cyst are distributed uniformly throughout cortex and medulla<br>- Cysts contain straw coloured fluid that may become haemorrhagic | |
| **Presentation:** usually occurs in III[rd] / IV[th] decade | |
| **Renal** | **Extra renal manifestation** |
| 1. Pain: due to infection (Pyelonephritis) / obstruction / sudden haemorrhage<br>2. Haematuria ♀<br>3. Nocturia: due to impaired concentrating ability<br>4. Nephrolithiasis (15-20%) ♀<br>5. Hypertension (75% adults and 25% children) : due to activation of rennin angiotensin system. ♀<br>6. Progressive decline in renal function – CRF | 1. Cysts: Liver (most common)<br>Spleen, pancreas and ovaries<br>2. Intracranial aneurysms<br>3. Colonic diverticular disease<br>4. Cardiac: Mitral valve prolapse / AR / TR |

**215. Answer is A (Berry Aneurysm in Circle of Willis):** *Harrison 15th/1600; 16th/1696; 17th/1798; Harrison 18th/p 2356 Chandrasoma Taylor3rd/700*

***Intracranial Berry aneurysms are important extrarenal associations of adult polycystic kidney disease.***

**Extra renal anomalies seen in patients with adult polycystic kidney disease.**

| GIT | CNS | Cardiac |
|---|---|---|
| • Cysts in Liver, Spleen, Pancreas<br>• Colonic diverticular disease | • Intracranial aneurysms (Berry) | • Mitral valve prolapse Q<br>• Aortic and tricuspid insufficiency |

*Cysts may also be seen in the ovary.*

**216. Answer is A (Lung):** *Harrison 15th/ 1600; Harrison 16th/1696; 17th/1798; Harrison 18th/p 2356 Robbins 7th/964*

***Cysts in lung are not associated with PCKD***

**Cysts in polycystic kidney disease may be seen in :**

- Liver : Hepatic cysts (50 – 70 %)
- Spleen
- Pancreas
- Ovaries

- *Most common extrarenal sites of cyst formation is the Liver* Q
- *Hepatic cysts occur in 50 – 70% of cases* Q
- *Cysts are generally asymptomatic and liver function is normal.* Q

**217. Answer is B (Hepatic cysts) :** *Urology secrets 3rd/134 Clinical pedicatric urology (2002)/ 657; Refer text below*

***Hepatic cysts are the most common extra renal manifestations of Adult polycystic kidney Disease***–*Urology secrets 3rd/134*

Confusion on the most common extra renal manifestation of APCKD

*Most standard text books mention Liver cysts as the most common extrarenal manifestation of Adult polycystic kidney disease*

*Urology secrets 3rd/134;*
*Adult and Pediatric Urology 4th/831*
*'Clinical Pediatric Urology'(2002) / 657*
*'Liver disease: Diagnosis & 'Management' (2000)/322*

*Few standard tetxbooks including Old edition of Harrisons (not mentioned in new editions) mention Colonic diverticular disease as the most common extrarenal manifestation of APCKD.*

*Harrisons 15th/1600 (Not in new edition)*
*First AID for USMLE STEP 1 (2006)/281*

**218. Answer is B (Presentation is Unilateral):** *Harrison 16th/ 1696; 17th/1797, 1798, Harrison 18th/p 2355, 2356 Robbins 7th/962, 963;Bailey 24th/1307*

- ***The presentation in Polycystic disease of kidney is characteristically bilateral***
  *- The bilateral enlargement can hardly be mistaken on routine examination – Bailey*
  *- USG and CT show multiple cysts in both kidneys - Bailey*
- The disease may present at any age but *the most common age of presentation is in the 3rd or 4th decade.*
- **Both the kidney are grossly enlarged and situated with multiple cysts.**
- Intracranial berry aneurysms are seen in 5-10 % of patients.

**219. Answer is A (Autosomal Dominant) :** *Nelson's 18th / 1706, Robbins 7th / 964; Harrison's 17th / 1799, Harrison 18th/p 2358, 2359 Clinical Pediatric Nephrology 2nd / 262*

***Childhood Polycystic Kidney Disease is synonymously used for Autosomal Recessive Kidney Disease.***

**Polycystic Kidney Disease**

| Adult Polycystic Kidney Disease | Childhood Polycystic Kidney Disease |
|---|---|
| *Also termed as Autosomal Dominant Polycystic kidney disease (ADPKD)* | *Also termed as Autosomal Recessive Polycystic kidney Disease (ARPKD)* |

**Childhood Polycystic kidney Disease / Autosomal Recessive PKD : Review**

Childhood Polycystic kidney disease is a rare developmental anomaly genetically distinct from Adult polycystic kidney Disease ***having an autosomal recessive inheritance***

Genetics

- *Autosomal Recessive inheritance*
- Defective gene is the PKHD1 (Polycystic kidney and Hepatic Disease 1)
- PKHD1 gene codes for a protein 'Fibrocystin' (defective protein in ARPKD)[Q]

Epidemiology

- Majority of patients present during infancy (first year of life)
- May present later in life (in young adults)

Presentation

- Presentation is variable and depends on age at presentation

| Respiratory Symptoms | Renal Features | Hepatic Features |
|---|---|---|
| Respiratory distress | • Hypertension<br>• Renal failure<br>• Enlarged kidneys (abdominal mass)<br>• Pyuria<br>• Proteinuria | • Hepatomegaly<br>• Features of portal Hypertension<br>-Esophageal varices<br>-Hypersplenism |

Associations

- **Maternal Oligohydramnios**
  Oligohydramnios may be present due to severe intrauterine kidney disease
- **Potter's syndrome**
  Most severely affected neonates may have Potter's syndrome due to oligohydramnios
- **Pulmonary Hypoplasia**
  *Pulmonary hypoplasia may result from severe oligohydramnios and as part of Potter's sequence*
  *'About 50% of affected neonates die of pulmonary hypoplasia' - Harrison's*
- **Congenital Hepatic fibrosis**
  *Congenital Hepatic Fibrosis is a peculiar type of hepatic fibrosis characterized by bland periportal fibrosis, and proliferation of well differentiated biliary ductules*
  **Hepatic cysts may be seen** (In almost all cases liver has cysts with portal fibrosis - Robbins)
- **Biliary Ductal Atresia**
  ARPKP is invariably associated with congenital hepatic fibrosis and various degrees of biliary ductal Atresia

Renal Pathology

- Kidney's are enlarged (invariably Bilateral)
- Numerous small cysts are present in kidney which give it ' Sponge like appearance'
- Cysts are primarily located in distal tubule and collecting duct
- ***Cysts may be discovered prenatally, at birth or later in life***

**220. Answer is C (Unilateral renal dysplasia):** *Sutton's Radiology 6th/ 1105; Nelson 17th/ 1784*

*The multicystic **dysplastic kidney** is the commonest form of **congenital cystic renal dysplasia**, and is due to complete uretric obstruction in fetal life. The condition is **usually unilateral**; bilateral disease is lethal.*

Cystic diseases of kidney in infants

- Dysplastic kidney (multicystic)
- Polycystic kidney (Autosomal Recessive; Autosomal dominant)
- Multilocular cystic nephroma

**Renal dysplasia. Multicystic kidney:**
*'It is the commonest cause of renal mass in infants' – Ghai 6th/ 467*

**221. Answer is D (Nephronopthisis) :** Refer previous question

***Presence of nocturnal enuresis, growth retardation (short stature) and renal failure (elevated urea and creatinine) without hematuria, edema or hypertension and the presence of small sized shrunken kidneys suggest the diagnosis of Nephronophthysis.***

The diagnosis of Nephronophthysis should be considered if a child presents with:

- *Polyuria (or nocturnal enuresis), Polydypsia and Urinary sodium loss (hyponotremia)*
- *Growth retardation (short stature), and anemia*
- *Renal insufficiency (elevated BUN/creatinine) without hematuria, proteinuria, edema or hypertension*
- *Normal or small sized kidney on USG*

Diagnostic Clues in the question

- Age = 12years (Juvenile Age group)
- Biochemical parameters

| Parameter | Normal value | Value in child | Inference |
|---|---|---|---|
| Urea | 10-40mg/dl | 112mg/dl | Elevated (Renal failure) |
| Creatinine | <1.5 mg/dl | 6mg/dl | Elevated (Renal failure) |
| Sodium | 136-146 meq/dl | 119 meq/dl | Hyponatremia (salt wasting) |

- Symptoms: Nocturia (polyurea) and short stature (Growth Retardation)
- **Features of Renal Failure :** No Hematuria, No Hypertension, No significant proteinuria
- USG: Bilateral small kidneys.

***The presence of Nocturia, Growth retardation and onset of Renal feature at an age <20 years without hematuria, hypertension, and edema along with shrunken kidney on USG suggests – the diagnosis of Nephronophysis.***

Cystic Disease of Renal Medulla

| Nephrophtysis – Medullary cystic kidney | Medullary Sponge kidney |
|---|---|
| Both these conditions may progress to end stage Renal disease and present with similar clinical features. | This is a relatively benign condition |

| Nephrophthysis | Medullary Cystic kidney |
|---|---|
| • Autosomal Recessive | Autosomal dominant |
| • Age of onset in 1st decade (Juvenile) | Age of onset in 3rd or 4th decade (Adult) |
| • Progression to ESRD occurs <20 years of age | • Progression to ESRD occurs >20 years to age |
| • Growth Retardation is present as it affects growing children | • Growth retardation is usually not associated as it affects adults |
| • Extra renal abnormalities are frequent and include *Retinitis pigmentosa* *Cerebellar Ataxia* *Hepatic fibrosis* *Skeletal abnormalities* | • Extra renal abnormalities are absent. |

**222. Answer is B (Nephronophthisis):** *Harrison 18th/p 2359 Harrisons 17th/1799*

***Repeated attacks of polyurea, salt wasting (hyponatremia), evidence of renal failure (elevated creatinine) and small size of kidneys suggests a diagnosis of Nephropthisis or Medulary cystic disease.***

***The presence of this condition in juvenile age group (8 years) favours a diagnosis of Nephrophthisis which is the single best answer of choice. (Medullary cystic kidney disease presents in adults in 3rd or 4th decade).***

## Juvenile Nephronophthisis

Chronic Tubulo interstitial Nephritis which uniformly progresses to End stage Renal Disease.

**Extrarenal Abnormalities**[Q]
- *Ritinitis Pigmentosa*
- *Cerebellar Ataxia*
- *Hepatic Fibrosis*
- *Skeletal Anomalies*

*Autosomal Recessive disease*[Q]

Pathology Triad
- Tubular Basement Membrane Disintegration
- Tubular cyst formation (Medullary Cyst)
- Tubulo interstitial inflammation

*Kidney size is normal or Reduced (shrunken)*[Q]

**Loss of Urinary Concentrating Ability**

*Polyurea*[Q] *Polydipsia*[Q] — *Nocturnal Enuresis*[Q]

*Low urinary osmolarity which does not increase after desmopressin administration*

**Salt wasting**
- *Hyponatremia*[Q]
- *Hypovolumia (dehydration)* [Q]
- *Hypotension (low BP)* [Q]

**Progressive Renal failure**

Because of loss of urinary concentrating ability and salt wasting, typical symptoms of renal failure do not occur until late in disease

*Edema, Hypertension, Hematuria and proteinuria do not occur until late in disease*
- *Anemia*[Q]
- *Growth Retardation*[Q]
- *Elevated BUN/creatinine*[Q]

**223. Answer is D (Biopsy):** *Harrison 17th/1800; CMDT 2005/899*

***Although ultrasonography and CT scan can be useful in making a diagnosis of medullary cystic disease, an open renal biopsy that ensures recovery of tissue from the corticomedullary junction is definitive.***

**224. Answer is C (Vesicouretrial reflux induced pyelonephritis):** *Pediatr Nephrol. 1993 Aug;7(4):361-4 The small scarred kidney in childhood ;. Risdon RA.*

*Renal scarring is most commonly a result of chronic pyogenic infection of the kidney or chronic pyelonephritis. Chronic pyelonephritis occurs only in patients with major anatomic abnormalities, such as obstructive uropathy, struvite calculi, or,* ***most commonly, VUR (in 30 to 45% of young children with symptomatic UTI).*** *- Mercks manual (http://www.merck.com/mrkshared/mmanual/section17/chapter227/227a.jsp)*

***'In children < 10 yr, about 30 to 50% of UTIs are associated with vesicoureteral reflux (VUR) which can lead to*** *renal scarring* ***and renal insufficiency if not treated'*** *– Merck's manual*

***Remember*** *: Renal tuberculosis is always secondary to some primary focus elsewhere in body and occurs later in life then other forms (commonly around 20-40 years age group.)*

**225. Answer is A (One year of age) :** *Paediatrics Urology, Gear Heart / 16*

*"Normal adult kidney can produce urine with an osmolality of greater than 1000 m Osm/kg water. The healthy new born infant, subject to water deprivation for 10-14 hours can achieve an osmolality of only 500-700 m osm / kg.* ***This value increases gradually during the first few months and approximates to the adult value by about one year of age."***

## Renal Tumours

**226. Answer is A (Clear cell type):** *Harrison 17th/592; Robbins 7th/1016*

***Clear cell carcinomas are the most common histological type of Renal cell carcinoma.***

| Carcinoma Type | Frequency | Place of origin | Cell of origin | Cytogenetics | Growth Pattern |
|---|---|---|---|---|---|
| Clear cell | ***60%*** | ***Cortex*** | ***Proximal tubule*** | ***3p-*** | Acinar or sarcomatoid |
| Papillary | 5-15% | Cortex | Proximal tubule | *+7, +17, -Y* | Papillary or sarcomatoid |
| Chromophobic | 5-10% | Cortex | Cortical collecting duct | ***Hypodiploid*** | Solid, tubular, or sarcomatoid |
| Oncocytic | 5-10% | Cortex | Cortical collecting duct | Undetermined | Tumor nests |
| Collecting duct | < 1% | Medulla | Medullary collecting duct | Undetermined | Papillary or sarcomatoid |

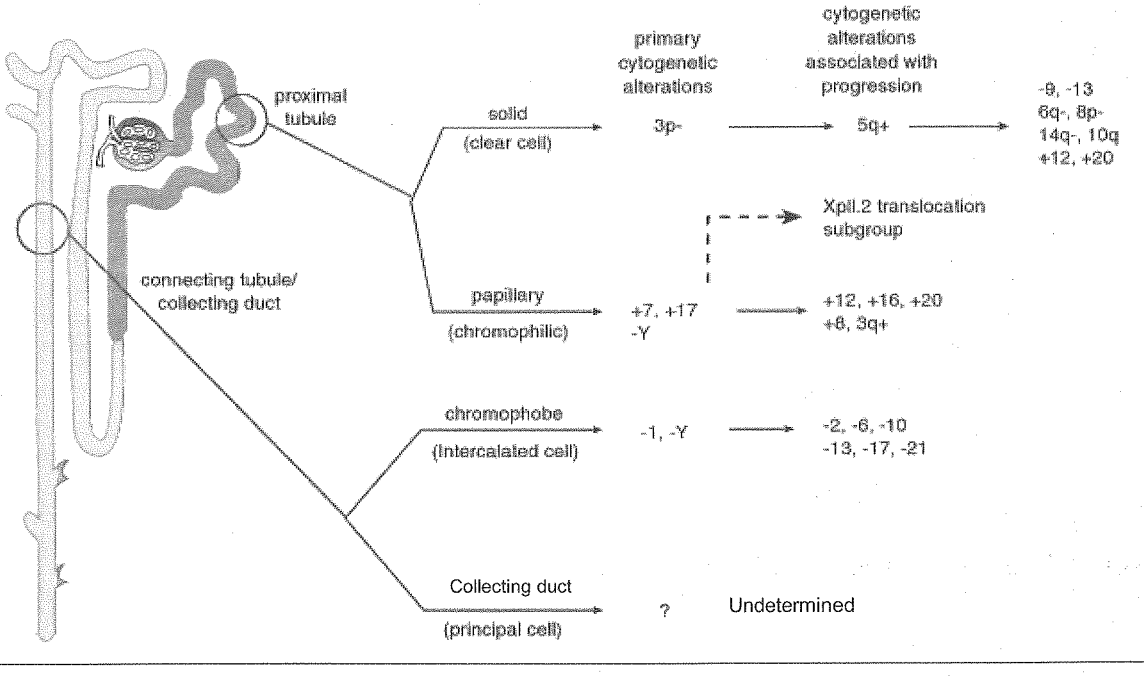
**227. Answer is D (Monosomy of 1 and y):** *Harrison's 17th/592, Urological Surgical Pathology' by Bostwick & Chang 2nd/96, 'The kidney' by Vize, Woolf & Bard 1st (2003)/454, 'Renal cell carcinoma' by Campbell & Rini 1st (2009)/42,43*

***Chromophobe variants of renal cell carcinoma are charachterized by widespread / extensive chromosomal losses resulting in monosomy or hypodiploid DNA index. This includes loss of chromosome 1 and Y.***

*'The abnormalities most consistently observed have been multiple losses of whole chromosomes, most frequently 1, 2, 6, 10, 13, 17, 21 and the Y chromosome' – Urological Surgical Pathology*

**Classification of epithelial neoplasms arising from the kidney**

| Carcinoma Type | Cell of Origin | Cytogenetics |
|---|---|---|
| Clear cell | Proximal tubule | 3p deletions (3p-), VHL gene mutations, 5q gains |
| Papillary | Proximal tubule | Trisomy of chromosome 7 and 17 (+7, +17)<br>Loss of Y chromosome (-Y) |
| ***Chromophobe*** | ***Cortical collecting duct*** | ***Hypodiploid / Monosomy***<br>***Loss of multiple chromosomes 1, 2, 6, 10, 13, 17, 21 & Y*** |
| Oncocytic | Cortical collecting duct | Undetermined<br>Either karyotypically normal or contain limited number of karyotypic abnormalities including -1, -Y and translocations involving chromosme II |
| Collecting duct | Medullary collecting duct | Undetermined<br>Losses of multiple chromosomes 1, 6, 14, 15 & 22 |



**228. Answer is B (Chromosome-3):** *Harrison 15th/ 607; Harrison 17th/ 592 Harrison 18th/p 793 Robbins 6th/ 993*

***Presence of painless haematuria with balottable mass in right flank in this forty years old male suggests diagnosis of renal cell carcinoma.*** *The most common histological variant 'clear cell carcinome' is associated with a defect in chromosome 3.*

**Features of three major histological variants of renal call carcinoma:**

| Clear cell carcinoma (Non papillary) | Papillary carcinoma | Chromophobe renal carcinoma |
|---|---|---|
| • Most common Q type Q (70-80%)<br>• Cells have clear Q or granular cytoplasm and are non papillary<br>• Defect lies in chromosomes 3 Q | • Second most common type (10-15%)<br>• Papillary Q growth pattern is characteristic (clear cell not seen)<br>• Psammoma bodies may be present<br>• Most common cytogenetic abnormality are<br>- trisomy of chromosome 7, 16 & 17 and loss of Y in male patients in sporadic form<br>- trisomy 7 in familial form<br>• Q Striking characteristic of tumor is: **Tendency to invade the renal vein** and grow as a solid column of cells within the vessels. Extension may produce a continuous cord of tumor in IVC and even in the right side of heart. | • Least common (5%)<br>• Pale eosinophilic cytoplasm<br>• Multiple chromosomal losses and extreme haploploidy |

**229. Answer is D (Radiosensitive):** *Harrison 17th/592, 593; Harrison 18th/p 793 CMDT 2008/1430, 1437; 2009/1463-1464; Robbins 7th/1016-1018; Smith's Urology 16th/357, 349; Bailey 24th/1332*

***Renal cell carcinoma is a relatively radioresistant tumor.***

**Renal cell carcinoma originates in the Renal cortex**

*'Renal cell carcinoma originates in the Renal cortex and tends to grow out into perinephric tissue causing the typical bulge or mass effect that aids in their detection by diagnostic imaging studies' – Smith's Urology*

**Renal Cell carcinoma are adenocarcinomas** *(Robbins 7th/1016)*

*Histologically Renal cell carcinoma is most often a mixed adenocarcinoma – Smith's Urology*

**Renal cell carcinomas may present with varicocele**

*'Renal cell carcinomas may present with Rapidly developing varicocele. Varicocele is usually observed on the left side. This occurs because left gonadal vein is obstructed where it joins the left renal vein.*

**Renal cell carcinomas are Relatively Radioresistant tumors**

*Renal cell carcinomas are generally considered radioresistant tumors*

Role of Radiotherapy in renal Cell carcinoma

- *Preoperative Radiation has shown no impact on survival*
- Postoperative Radiation has also shown no evidence of improved survival but may be used as it shows improvement in local control.
- *Palliative Radiotherapy has been shown to be effective in metastatic disease to brain, bone and lungs.*

**230. Answer is C (More common in female):** *Harrison 18th/p 793 Harrison 17th/592*

***Renal cell carcinoma is more common in males.***

**Renal cell carcinoma is more common in males**

*The male to female ratio of RCC is 2:1*

**Renal cell carcinoma arises from the proximal tubule**

*'RCC arise form the proximal tubular epithelium as evidenced by electron microscopy' – Smith's Urology 16th/349*

- *RCC arise most commonly from Renal cortex*
- *RCC originates most commonly from proximal renal tubular epithelium*
- *RCC more often arises from the 'poles' particularly the upper pole*

**Renal cell carcinoma may invade the Renal vein**

*Renal cell carcinoma may extend directly into the renal vein and inferior vena acav*

| | |
|---|---|
| Stage III A Disease | Tumor invades main renal vein or IVC |

**Renal cell carcinoma present with varicocele**

*'Renal cell carcinomas may present with Rapidly developing varicocele. Varicocele is usually observed on the left side. This occurs because left gonadal vein is obstructed where it joins the left renal vein.*

231. **Answer is B (Hypertension):** *Harrison 18th/p 793 Harrison 17th/592*

***Hypertension may be seen in patients with Renal cell carcinoma but it does not form part of the classically described triad.***

Classic Triad of Renal cell carcinoma (seen in 10-20% of patients)

- *Hematuria (Gross)*
- *Pain (Abdominal / Flank)*
- *Mass (Abdominal / Flank)*

232. **Answer is None (All may be seen):** *Harrison 18th/p 793, 2382 Harrison 17th/592; 1815*

***Renal cell carcinoma may present with Polycythemia (Erythrocytosis), Hypertension, Hematuria and Renal vein thrombosis.***

**Polycythemia (Erythrocytosis), Hypertension, Hematuria are signs of Renal Cell Carcinoma.** *(Harrison 17th/592)*

Signs and symptoms in patients with renal cell cancer

| Presenting Sign or Symptom | Incidence, % |
|---|---|
| *Classic triad: hematuria, flank pain, flank mass* | 10-20 |
| ***Hematuria*** | 40 |
| *Flank pain* | 40 |
| *Palpable mass* | 25 |
| *Weight mass* | 33 |
| *Anemia* | 33 |
| *Fever* | 20 |
| ***Hypertension*** | 20 |
| *Abnormal liver function* | 15 |
| *Hypercalcemia* | 5 |
| ***Erythrocytosis*** | 3 |
| *Neuromyopathy* | 3 |
| *Amyloidosis* | 2 |
| *Increased erythrocyte sedimentation rate* | 55 |

**Secondary Renal Vein Thrombosis may be seen due to invasion by Renal Cell Carcinoma** *(Harrison 17th/1815)*

Causes of Renal Vein Thrombosis

- *Trauma*
- *Extrinsic compression (Lymphnode, tumor, aortic aneurysm)*
- ***Invasion by Renal cell carcinoma***
- *Dehydration*
- *Nephrotic syndrome*
- *Pregnancy or oral contraceptives*

233. **Answer is None or D (None or Cushing;s syndrome):** *Harrison 18th/p 793 Harrison 17th/592; Robbin's 7th/1018; Smith's Urology 16th/351*

*Amongst the options provided, Cushing's syndrome is the least common paraneoplastic syndrome associated with Renal cell carcinoma, and hence the single best answer of exclusion.*

*Note that while Harison's textbook does not include Cushing's syndrome in the list of paraneoplastic syndromes associated with Renal cell carcinoma, this condition is clearly mentioned as an associated paraneoplastic syndrome in other standard textbooks like Robbin's and Smith's Urology.*

Paraneoplastic Syndromes is Renal Cell Carcinoma

| Characteristic Paraneoplastic Syndromes (common) | Other Paraneoplastic Syndromes (Less common / Not characteristic) |
|---|---|
| • ***Erythrocytes/Polycythemia*** (due to ↑ed erythropoietin)<br>• ***Hypercalcemia*** (due to ↑ed parathyroid related peptide)<br>• ***Hypertension*** (due to ↑ed rennin production )<br>• *Non metastatic Hepatic Dysfunction (Stauffer syndrome)* (due to ↑ed granulocyte-macrophage colony stimulating factor) | • Cushing's syndrome (due to ↑ ACTH production)<br>• Galactorrhea (due to ↑ed prolactin production)<br>• Hypoglycemia (due to ↑ed Insulin)<br>• Gynaecomastia & decreased libido (due to ↑ gonadotropins)<br>• Hirsuitism, amenorrhea and male pattern balding (due to ↑ gonadotropins)<br>• Amyloidosis<br>• Leukemoid Reaction and Eosinophilia<br>• Dysfibrinogenemia |

**234. Answer is B (Lungs):** *Smith's Urology 16th/349*

*'The most common site of distant metastasis (in RCC) is the lung' – Smith's Urology 16th/349*

**235. Answer is B (IVC involvement indicates inoperability):** *Harrison 16th/542; Harrison 17th/593 Harrison 18th/p 795*

*Extension of tumor into IVC does not indicate inoperability.*

*'Extension into renal vein or inferior vena cava **does not preclude resection** even if cardiopulmonary bypass is required. Half of these patients have prolonged survival' - Harrison*

**236. Answer is C (Arthogryposis multiplex congenita):** *Robbin's 7th/604, 605; Ghai 6th/574*

*Arthrogryposis multiplex congenita is not associated with Wilm's tumor.*

**Wilm's Tumor**

The risk of Wilm's tumor is increased in associations with at least three recognizable groups of congenital malformations associated with distinct chromosomal loci

| WAGR syndrome | Denys Drash Syndrome | Beckwith Wiedemann Syndrome |
|---|---|---|
| Characterized by:<br>• *Wilm's tumor*<br>• ***Aniridia***<br>• *Genital Anomalies*<br>• *Retardation (Mental)* | Characterized by:<br>• *Gonadal Dysgenesis* ***(male pseudohermaphroditism)***<br>• *Early onset nephropathy (diffuse mesangial sclerosis/renal failure)* | Characterized by:<br>• *Organomegaly*<br>• *Macroglossia*<br>• ***Hemihypertrophy***<br>• *Omphalocele*<br>• *Adrenal cytomegaly (Abnormal large cells in Adrenal cortex)* |

**237. Answer is B (Abdominal lump):** *Robbin's 7th/506; Ghai 6th/574*

*Most common presentation of Wilm's tumor is an asymptomatic Abdominal Mass.*

**238. Answer is D (Radiosensitive):** *Bailey 23rd/1196; Nelson 18th/2142; Ghai 6th/574, 575; Robbin's 7th/506*

***Wilm's tumor is both chemosensitive and Radiosensitive*** *(unlike renal cell carcinoma which is considered radioresistant and chemoresistant)*

**Wilm's tumor is associated with a good prognosis**
*The prognosis of Wilm's tumor is currently very good and excellent results are obtained with a combination of chemotherapy & nephrectomy.*

**Most common site of Metastasis in Wilm's Tumor is Lungs**
*Metastasis occurs early, mainly by the blood stream to the lungs.*
*Liver and bone metastasis are rare and brain metastasis even more so.*

**Wilm's tumor may be bilateral** (not always unilateral)
*Wilm's tumor may arise in one or both kidneys.*
*The incidence of bilateral Wilm's tumor is 7% - Nelson*

**239. Answer is C > A (Histology > Stage of disease):** *Devita 6th/2177*

*Both stage of the tumor and the histological grade have been described as the most important determination of prognosis, in different texts. If we have to choose a single best option, 'Histology' is the single best answer.*
***'The histology of Wilm's tumor was identified as the most important determinant of prognosis'*** *- Devita 6th/2177*

**240. Answer is B (International Society of Pediatric Oncology-SIOP) :** *Devita's 8th / 2051 , Schwartz 8th / 1509*

***The post-chemotherapy based staging system is the 'SIOP' staging system developed by the International society of pediatric oncology.***

Two Staging Systems are currently being used for the staging of Wilm's Tumor

| Pre-chemotherapy Staging System | Post-chemotherapy Staging System |
|---|---|
| • *Developed by the National Wilm's Tumor staging Group (NWTSG) (NWTSG – Staging system)* | • *Developed by the International Society of Pediatric Oncology (SIOP) (SIOP – Staging system)* |
| • This staging system is widely used in North America and Canada | • This staging system is widely used in Europe |
| • *'NWTSG' approach involves employment of 'primary Surgery'. Chemotherapy with or without Radiation therapy is given after surgery* | • 'SIOP' Approach involves employment of preoperative chemotherapy without histological confirmation of Wilm's tumor. (Primary chemotherapy for all patients regardless of extent) |
| • ***Staging is done at time of surgery (Pre – chemotherapy)*** | • ***Staging is done at time of surgery (Post-chemotherapy)*** |
| • Primary advantage is more accurate staging | • Primary advantage is easier surgical removal of tumor with decreased tumor rupture due to shrinkage of tumor by preoperative chemotherapy |
| Primary Surgery (Nephrectomy)<br>↓<br>**Staging (at surgery)**<br>**(Pre-chemotherapy staging)**<br>↓<br>Postoperative Chemotherapy / Radiation | Primary Chemotherapy (Preoperative)<br>↓<br>Surgery (Nephrectomy)<br>↓<br>**Staging (at surgery)**<br>**(Post-chemotherapy staging)**<br>↓<br>Postoperative chemotherapy / Radiation |

Both Staging Approaches (NWTSG and SIOP) have improved survival for patients with Wilm's tumor Success rates of treatment with both approaches are comparable

## Hepatorenal Syndrome

**241. Answer is A & B (urine Na < 10 meq/l and Normal Renal Histology):** *Walker's Pediatric Gastrointestinal Disease 5th/1140*

***Hepatorenal syndrome is associated with normal renal histology and supported by a urine sodium excretion < 10meq/L***

Hepatorenal syndrome

- Hepatorenal syndrome is defined as a state of functional renal failure (Reduced GFR) in patients with severe liver disease
- ***Structurally /Histologically the kidneys are normal and recover function after successful liver transplantation.***
- The pathogenetic hallmark of hepatorenal syndrome is intense renal vasoconstriction with coexistent systemic vasodilatation
- The diagnosis of hepatorenal syndrome is considered in accordance with the following diagnostic criteria.

| Diagnostic of Hepatorenal Syndrome |
|---|
| **Major criteria** |
| • *Low glomerular filtration rate, as indicated by serum creatinine > 1.5 mg/dL or 24-hr creatinine clearance < 40 mL/min* |
| • *Absence of shock, ongoing bacterial infection, fluid losses, and current treatment with nephrotoxic drugs* |
| • *No sustained improvement in renal function (decrease in serum creatinine to 1.5 mg/dL or increase in creatinine clearance to 40 mL/min) after diuretic withdrawal and expansion of plasma volume with 1.5L of a plasma expander* |
| • *Proteinuria <500 mg/dL and no ultrasonographic evidence of obstructive uropathy or parenchymal renal disease* |
| **Additional criteria** |
| • *Urine volume < 500 mL/d* |
| • *Urine sodium < 10 meq/L* |
| • *Urine osmolality greater than plasma osmolality* |
| • *Urine red blood cells <50/high- power field* |
| • *Serum sodium concentration < 130 mEqL* |
| Note: All major criteria must be present for the diagnosis of hepatorenal syndrome. Additional criteria are not necessary for the diagnosis but provide supportive evidence. |

**242. Answer is C (Urine osmolality is lower than plasma osmolality):** *Washington manual of Medical Therapeutics 32nd/506*

***Hepatorenal syndrome is associated with urine osmolality greater than plasma osmolality (and not lower than plasma osmolality)***

*Creatinine clearance < 40 ml/minute and poor response to volume expansion are major diagnostic features of hepatorenal syndrome while urinary sodium of less than 10 mmol/L is an additional criteria that provides supportive evidence.*

| Diagnostic of Hepatorenal Syndrome |
|---|
| **Major criteria** |
| • *Low glomerular filtration rate, as indicated by serum creatinine > 1.5 mg/dL or 24-hr creatinine clearance < 40 mL/min* |
| • *Absence of shock, ongoing bacterial infection, fluid losses, and current treatment with nephrotoxic drugs* |
| • *No sustained improvement in renal function (decrease in serum creatinine to 1.5 mg/dL or increase in creatinine clearance to 40 mL/min) after diuretic withdrawal and expansion of plasma volume with 1.5L of a plasma expander* |
| • *Proteinuria <500 mg/dL and no ultrasonographic evidence of obstructive uropathy or parenchymal renal disease* |
| **Additional criteria** |
| • *Urine volume < 500 mL/d* |
| • *Urine sodium < 10 meq/L* |
| • *Urine osmolality greater than plasma osmolality* |
| • *Urine red blood cells <50/high- power field* |
| • *Serum sodium concentration < 130 mEqL* |
| Note: All major criteria must be present for the diagnosis of hepatorenal syndrome. Additional criteria are not necessary for the diagnosis but provide supportive evidence. |

**243. Answer is A > C (The creatinine clearance is > 40 ml/min) :** *Washington Manual of medical Therapeutics 32nd/506, Refer previous question.*

***Hepatorenal syndrome is associated with creatinine clearance < 40 ml/min which is a major criteria in the diagnsis of hepatorenal syndrome and the single best answer of choice***

*Hepatorenal syndrome is also associated with a urine osmolaity that is higher (and not lower) than plasma osmolality. However this is an additional or supportive criteria that is not necessary for diagnosis and hence this is not the answer of choice.*

## Rhabdomyolysis

**244. Answer is A (Acute Renal Failure):** *Refer text below*

***Acute Renal failure is an established complication of crush syndrome.***

*Acute Renal Failure is usually caused by a combination of hypovolemia and release of nephrotoxic substances into the circulation such as myoglobin*

*Crush syndrome is associated with hypocalcemia and hyperphosphatemia*

**Crush Syndrome (Rhabdomyolysis)**
**(SystemicManifestation of severe crush injury)**

| Hypotension | Renal Failure (ARF) | Metabolic Complication |
|---|---|---|
| • Shock<br>• Compartment<br>• Syndrome | • Myoglobinuria<br>*Rhabdomyolysis results in the release of myoglobin, potassium phosphorus & creatinine into the circulation* | • Hyperkalemia<br>• ***Hypocalcemia***<br>• ***Hyperphosphatemia***<br>• Metabolic Acidosis<br>Cardiac arrhythmias may result secondary to metabolic comp. |

**Note –**
*Crush syndrome is associated with Hypocalcemia and not hypercalcemia. Systemic hypocalcemia results from inflow of calcium into muscle calls through leaky sarcolemmal membranes[Q].*

**245. Answer is B (Hyperphosphatemia):** *Current Critical Care Diagnosis and Treatment 3rd/326; Diseases of Kidney & urinary Tract 8th/1185*

***Rhabdomyolysis may be caused by hypophosphatemia and not by hyperphosphatemia.***

*'When severe and sustained hypophosphatemia can cause severe myopathy and rhabdomyolysis'.*
*– Current Diagnosis and Treatment in Neurology 1st/373*

**Selected Causes of Rhabdomyolysis (Incomplete list):**

| Physical Trauma |
|---|
| • Crush injury |
| • Heat stress |
| • Electrocution |
| • Exercise |
| • Hypothermia |
| • Malignant hyperthermia |
| • Neuroleptic malignant syndrome |
| • Severe burns |
| • Contact sports |
| • Direct muscle trauma |

| Anoxic injury |
|---|
| • Arterial occlusion |
| • Seizures |
| • Tetanus |
| • Compartment syndrome |
| • Delirium tremens |
| **Toxins** |
| • Ethanol |
| • Heroin |
| • Barbiturates |

| Metabolic |
|---|
| • Hypokalemia |
| • Hypophosphatemia |
| • Diabetic ketaoacidosis |
| • Diabetic hyperosmolar non ketotic coma |
| • Myxedemia |
| • Carnitine deficiency |
| • Hereditary muscle enzyme deficiency<br>-Phosphorylase deficiency (McArdle's disease)<br>-Phosphofructokinase deficiency<br>-α-Glucosidase deficiency<br>-Carnitine palmityltransferase deficiency<br>-Amylo-1,6-glucosidase deficiency |
| Infections |
| Inflammation |
| • Polymyositis |
| • Dermatomyositis |
| Poisons |
| • Snake, spider and insect venoms |

- Cocaine
- Amphetamine
- Benzodiazepines
- Phencyclidine
- HMG-CoA reductase inhibitors (statins)
- Fibric acid derivatives (clofibrate, gemfibrozil)
- Hemlock
- Salicylates
- Carbon monoxide
- Ethylene glycol
- Isopropyl alcohol
- Snake and insect venoms
- Succinylcholine
- Colchicine
- Propofol
- Para-phenylenediamine
- Colchicum autumnale (autumn crocus)
- Monensin

**246. Answer is E (All of the above):** *'Clinical Infectious Disease' by Schlossberg 1st (2008)/492, 493*

***Bacterial infections from clostridium species and streptococcus and envenomations from Russel Viper and Hornet may all cause rhabdomyolysis.***

**Infectious causes of Rhabdomyolysis**

Bacterial

| Gram-Positive bacteria |
|---|
| *Streptococcus pneumoniae* |
| *Staphylococcus aureus* |
| *Group B streptococcus* |
| *Streptococcus pyogenes* |
| *Listeria spp.* |
| *Staphylococcus epidermidis* |
| *Bacillus spp.* |
| ***Clostridium spp.*** |
| *Viridans streptococci* |
| *Streptococcus suis* |
| *β-hemolytic streptococci* |
| *Streptococcus pyogenes* |

| Gram-Negative bacteria |
|---|
| *Legionella spp.* |
| *Francesella tularensis* |
| *Salmonella spp.* |
| *Vibrio spp.* |
| *Brucella spp.* |
| *Escherichia coli* |
| *Herbicola lathyri* |
| *Klebsiella spp.* |
| *Aeromonas* |
| *Haemophilus influenza* |
| *Neisseria spp.* |

| Mycobacteria |
|---|
| *Intravesical instillation of BCG* |
| *Tuberculosis* |

Fungal / Protozoal and Helminthic

| Fungal |
|---|
| *Candida spp.* |
| *Aspergillus spp.* |
| *Mucor spp.* |

| Protozoal and Helminthic |
|---|
| *Plasmodium spp.* |
| *Toxoplasma gondii* |
| *Trichinosis* |

Miscellaneous infections causes

| Spirochetes |
|---|
| *Leptospira spp.* |
| *Borrelia burgdorferi* |

| Rickettsial |
|---|
| *Rickettsia conorii* |
| *Rickettsia tsutsugamushi* |
| *Ehrlichia equi* |
| *Ehrlichia chaffeensis* |
| *Coxiella burnetti* |
| *Anaplasma phagocytophilum* |

| Mycoplasma |
|---|
| *Mycoplasma pneumonia* |

Poisons

| Snakes | Spider and Insects |
|---|---|
| *South American rattlesnake* | ***Hornets*** |
| *Tiger snake* | *Wasps* |
| *Majove rattlesnake* | *Bees* |
| ***Russel viper*** | *Desert centipdede* |
| | *Redback spider* |
| | *Taipan* |

**247. Answer is C (Hyperthyroidism)**

***Hypothyroidism is a cause for Rhabdomyolysis and not hyperthyroidism***

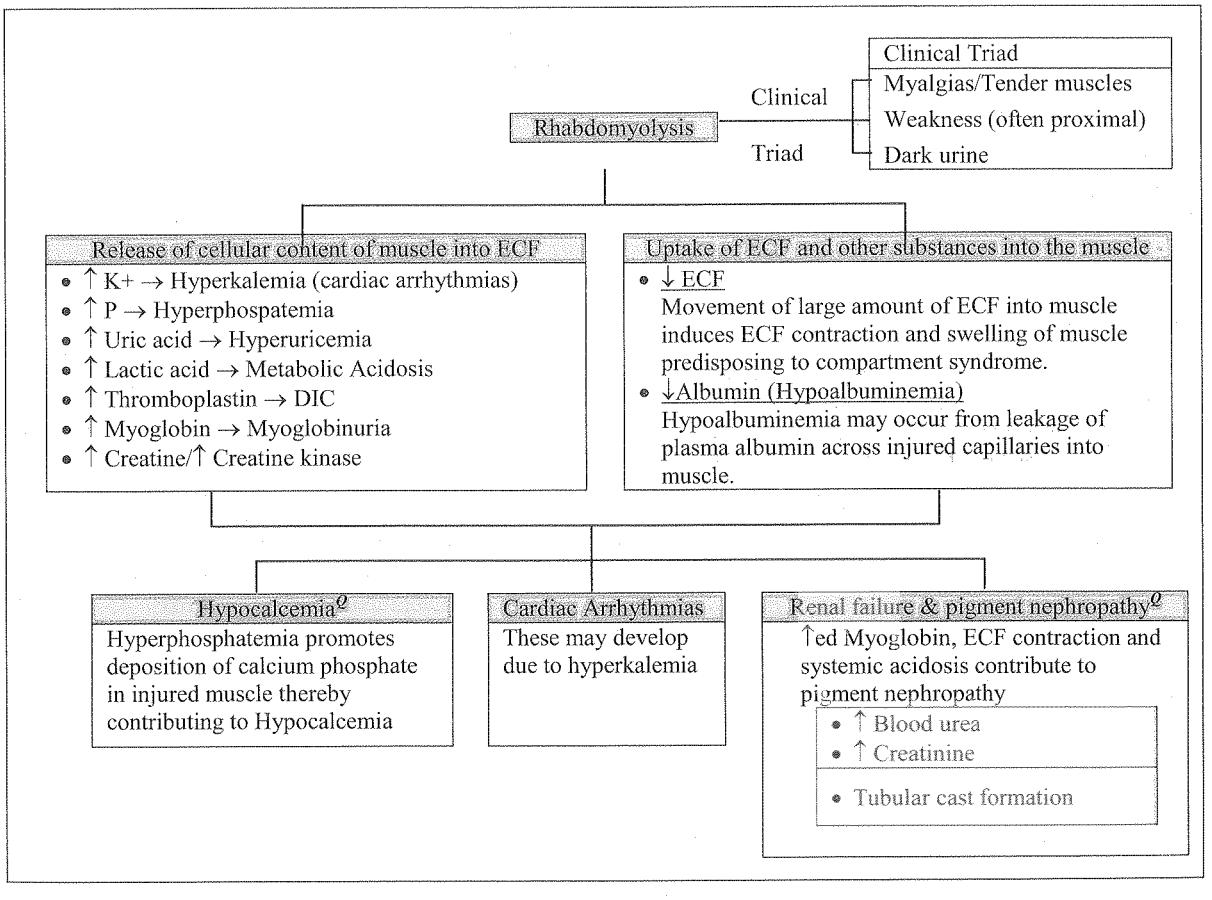
Metabolic causes of Rhabdomyolysis

*Hypokalcemia*
*Hypophosphatemia*
***Hypothyroidism (Myxoedema)***
*Diabetic ketoacidosis*
*Diabetic hyperosmolar non ketotic coma*
*Hereditary muscle enzyme deficiencies*
*Carnitine deficiency*

**248. Answer is C (Hypercalcemia):** *Primer on kidney disease 4th/310, 311*

***Rhabdomyolysis is associated with hypocalcemia and not hypercalcemia***

*Hyperphosphatemia promotes the deposition of calcium phosphate in injured muscle thereby contributing to hypocalcemia.*



**249. Answer is C (Hemoglobinuria):** *Refer previous question*

***Hemoglobinuria is not a feature of Rhabdomyolysis***

**Acute muscular weakness is seen in Rhabdomyolysis**

*'Pain and swelling of the involved muscles and weakness of limbs occur especially in proximal distribution'.*
*– Current Diagnosis and Treatment in Emergency Medicine 6th/650*

*'Acute proximal muscle weakness, pain, swelling, tenderness and cramping of affected muscles is the most frequent feature'. – Skeletal Muscle 1st (2002)/8*

**Myoglobnuria is a feature of Rhabdomyolysis**

*Rhabdomyolysis leads to leakage of Myoglobin from muscle into the plasma and from plasma into urine causing myoglobinuria. Rhabdomyolysis and Myoglobinuria reflect similar clinical conditions and are often grouped as Rhabdomyolysis – Myoglobinuria syndrome.*

**Rhabdomyolysis may present with Acute Renal failure**

*Acute Renal failure is the major potential complication of Rhabdomyolysis.*

## Tumor Lysis Syndrome

**250. Answer is B (Hypercalcemia):** *Harrison*

***Tumor Lysis syndrome is associated with Hypocalcemia and not Hypercalcemia.***

***Tumor Lysis syndrome:***

***It is a clinical entity characterized by destruction of large number of rapidly proliferating neoplastic cells following chemotherapy.***

*Rapid lysis of tumor cells after chemotherapy*
**(Tumor Lysis Syndrome)**[Q]

| | | |
|---|---|---|
| • *Release of uric acid* [Q] from rapid turn-over nucleic acids. ***Hyperuricemia***[Q] | • Release of intracellular Phosphate ***Hyperphosphatemia***[Q] | • Release of intracellular Potassium ***Hyperkalemia*** [Q] |
| • Uric acid may precipitate in tubules, medulla and collecting duct | • Increased phosphate drives calcium into bone ***Hypocalcemia*** [Q] | • Predisposes to ***Arrhythmias*** [Q] |
| • ***Renal failure*** [Q] | • Calcium phosphate may deposit in renal tubules ***- Renal failure*** | ***Acidosis*** [Q] is also a feature and results in part from deranged oxidative metabolism ***-Lactic acidosis***[Q] |

**251. Answer is B (Hypercalcemia):** *Harrison*

***Tumor Lysis syndrome is characterized with hypocalcemia and not hypercalcemia.***

**252. Answer is D (Serum uric acid):** *Harrison's 18th/2274*

***Serum Uric Acid Levels are used to predict prognosis for return of renal function a patient with tumour lysis syndrome is. Renal function recovers after the uric acid level is lowered to <10 mg/dL.***

## Bartter's Syndrome and Gitelman's Syndrome

**253. Answer is B (Hypokalemia):** *Refer Text below*

***Bartter's Syndrome is characterized by Chloride resistant Metabolic Alkalosis and Hypokalemia without Hypertension. Urinary Calcium Excretion is typically increased .***

| **Bartter's Syndrome** (Resembles Loop Diuretics) |
|---|
| **Inheritance** |
| *Autosomal recessive disorder.* |
| **Pathophysiology** |
| *Genetic defect involving the transporter's in the thick ascending limb of the glomerulus.*<br>*Defects in Na-K-2Cl cotransporter, K or Cl channels result in lack of concentrating ability*<br>***Resembles Loop Diuretics*** |
| **Clinical presentation:** |
| *History of polyuria and polydipsia*<br>*Hypokalemic metabolic alkalosis without Hypertension*<br>*Presents early in life, often with sensorineural deafness (has to do with potassium-secreting dark cells of inner ear), triangular facies with drooping mouth and large eyes and pinnae, and renal failure.* |
| **Laboratory data** |
| *Chloride resistant metabolic alkalosis and Hypokalemia*<br>***Normal serum magnesium.***<br>*Increased Urinary Calcium Excretion (Hypercalciuria so at risk for **kidney stones**)* |

**254. Answer is C (Genetic defect in Bartter Syndrome involves the transport proteins in the distal tubule):** *Refer text below*

***Genetic defect in Bartter Syndrome is located in the thick ascending limb of the loop of Henle.***

| *Features* | *Bartter Syndrome*<br>*(Mimics Loop Diuretics)* | *Gitelman's Syndrome*<br>*(Mimics Thiazide Diuretics)* |
|---|---|---|
| *Inheritance* | • ***Autosomal recessive disorder.*** | • ***Autosomal recessive disorder*** |
| *Pathophysiology* | • ***Genetic defect in the thick ascending limb of the Loop of Henle***<br>• *Defects in Na-K-2Cl co-transporter, K or Cl channels result in lack of concentrating ability* | • ***Genetic defect in the distal tubule***<br>• *Defect in Na-Cl cotransporter in the distal tubule* |
| *Age of Presentation* | • *Early in life.* | • *Late childhood or early adulthood.* |
| *Clinical presentation:* | • *No Hypertension*<br>• *Polyuria and polydipsia common*<br>• *Neuromuscular symptoms are uncommon or mild*<br>*Often presents with sensorineural deafness, triangular facies with drooping mouth, large eyes and pinnae, and renal failure.* | • *No Hypertension (Can see lower than average blood pressure due to salt wasting).*<br>• *Polyuria and nocturia in 50-80%.*<br>• *Often present with neuromuscular symptoms such as muscle cramping and spasms, significant fatigue.* |
| *Lab data:* | • *Chloride resistant metabolic alkalosis*<br>• *Hypokalemia*<br>• ***Normal serum magnesium (may be low).***<br>• ***Increased Urinary Calcium Excretion***<br>*(Hypercalciuric so at risk for kidney stones or nephrocalcinosis)* | • *Chloride-resistant metabolic alkalosis*<br>• *Hypokalemia.*<br>• ***Hypomagnesemia***<br>• ***Decreased Urinary calcium excretion***<br>• *Hypocalciuric so no increased risk of kidney stones or nephrocalcinosis)* |
| *Renal PGE2 production* | • *Increased* | • *Normal* |

*Note that serum calcium tends to be normal in patients with Gitelman's Syndrome due to lower PTH levels, Increased plasma renin and aldosterone/ K+ ratio.*

**255. Answer is A (Bartter Syndrome):** *Refer text above*

***Hypokalemic Metabolic Alkalosis with Hypercalciuria in a patient with normal blood pressure suggests a diagnosis of Bartter Syndrome.***

*Hypokalemic metabolic alkalosis with normal blood pressure may be seen in both Bartter Syndrome and Gitelman's Syndrome. Presence of Nephrocalcinosis from Increased Urinary excretion of Calcium is typically seen in Bartter's Syndrome and distinguishes Bartter's Syndrome from Gitelman's Syndrome (Decreased Urinary Calcium Excretion). Liddle's Syndrome also causes Hypokalemic metabolic alkalosis but this disorder is typically associated with Hypertension (Blood Pressure is elevated)*

| *Presentation* | *Diagnosis* |
|---|---|
| *Hypokalemic Metabolic alkalosis* ***with Hypertension*** | *Liddle's Syndrome* |
| *Hypokalemic Metabolic Alkalosis* ***without Hypertension*** | *Bartter Syndrome (Increased Urinary Ca Excretion)*<br>*Gitelman's Syndrome (Decreased Urinary Ca Excretion)* |

| ***Important Differences Between Bartter Syndrome and Gitelman's Syndrome*** | | |
|---|---|---|
| ***Feature*** | ***Bartter Syndrome*** | ***Gitelman's Syndrome*** |
| ***Location of kidney defect*** | Ascending loop of Henle<br>(Mimics effects of loop diuretics) | Distal tubule<br>(Mimics effects of thiazides) |
| *Urinary Calcium excretion* | Normal or increased, commonly with nephrocalcinosis | Decreased |
| ***Serum Mg level*** | Normal Magnesium levels (May be decreased) | Decreased, sometimes greatly |
| ***Renal prostaglandin E2 production*** | Increased | Normal |
| ***Usual age at presentation*** | Before birth to early childhood, often with intellectual disability and growth disturbance | Late childhood to adulthood |
| *Neuromuscular symptoms (e.g., muscle spasms, weakness)* | Uncommon or mild | Common |

**256. Answer is B (Hypermagnesemia):** *Harrison 18th/p2360 Harrisons 17th/1801*

***Bartter's syndrome is associated with Hyomagnesemia and not Hypermagnesemia.***

## Contrast Nephropathy

**257. Answer is C (Hydration with Normal Saline):** *Evidence-Based Practice of Critical Care: Expert Consult(Elsevier Health Sciences)2010/ 384,385; Strategies to Reduce the Risk of Contrast-Induced Nephropathy : The CIN Consensus Working Panel*
*(Link: http://www.nimbot.com/Med/Articles/RCIN/CIN%20Consensus%20Strategies.pdf)*

***Despite extensive study of a variety of agents for renal protection, use of low or iso-osmolar contrast agents and IV hydration with normal saline or sodium bicarbonate are the only strategies that have been shown to be effective in the reduction of Contrast Induced Nephropathy (CIN) in those at risk****. N-Aceytl-Cystine (NAC) continues to be the most widely used pharmacologic agent however its effectiveness remains unproven.*

Interventions to prevent Contrast Induced Nephropathy
(Consensus Statement from CIN Working Panel)

| Adequate Hydration | Use of Pharmacological Agents | Prophylactic Hemodialysis or Hemofiltration |
|---|---|---|
| • Adequate intravenous volume expansion with isotonic crystalloid for 3–12 hours before the procedure and continued for 6 –24 hours afterward can lessen the probability of CIN in patients at risk | • There are no Pharmacological Agents with robust and consistent trial evidence to support clinical use in patients at risk for CIN.<br>• However, the CIN Consensus Working Panel agreed that in patients at increased risk for CIN (ie, with an eGFR< 60 mL/min per 1.73 m2) consideration could be given to prophylactic treatment with any of the agents that have given promising results, specifically theophylline, statins, ascorbic acid, or PGE1. These agents deserve further evaluation. | • Prophylactic hemodialysis or hemofiltration has not been validated as an effective strategy.<br>• Although hemodialysis is not useful for reducing the risk for CIN, the CIN Consensus Working Panel recommends that for patients with severe renal impairment who require contrast medium administration, preparation for the procedure should include planning for hemodialysis in the event that CIN occurs despite appropriate precautions.<br>• Hemofiltration requires further validation. |

N-Acetyl-Cysteine(NAC) is one of the most commonly used agents given before contrast media in patients with renal impairment in an effort to minimize the risk of Contrast Induced Nephropathy (CIN). Use of this agent is attractive due to its wide availability, ease of administration, and low cost. However, despite extensive research, any benefit offered by NAC remains unclear. In fact, a CIN Consensus Working Panel reported in 2006 that NAC is not consistently effective in reducing the risk for CIN. NAC is most commonly administered as a dose of 600 to 1200 mg by mouth twice daily on the day before the procedure and the day of the procedure. However, there are currently no data to guide choice of an optimum oral or IV acetylcysteine regimen. Several Studies on NAC for Contrast Induced Nephropathy have produced conflicting results . Based on current evidence the use of NAC for Contrast Induced Nephropathy cannot be recommended.

| | |
|---|---|
| NAC | Despite extensive research, any benefit offered by NAC remains unclear.<br>Routine use of NAC for Contrast Induced Nephropathy cannot be recommended. Given the lack of compelling evidence of efficacy, contrast studies should not be delayed to administer NAC. |

**258. Answer is D (Furosemide):** *Evidence-Based Practice of Critical Care: Expert Consult(Elsevier Health Sciences)2010/ 384,385; Strategies to Reduce the Risk of Contrast-Induced Nephropathy : The CIN Consensus Working Panel (Link: http://www.nimbot.com/Med/Articles/RCIN/CIN%20Consensus%20Strategies.pdf)*

***Use of Furosemide may be potentially detrimental in patients with Contrast Induced Nephropathy (CIN) and is not recommended.***

The CIN Consensus Working Panel : Summary: Conclusion

| **Positive results** (Potentially beneficial) | **Neutral results** (No consistent effect) | **Negative results** (Potentially detrimental) |
|---|---|---|
| • *Theophylline/aminophylline*<br>• *Statins*<br>• *Ascorbic acid*<br>• ***Prostaglandin $E_1$*** | • ***N-acetylcysteine (NAC)***<br>• ***Fenoldopam***<br>• *Dopamine*<br>• *Calcium channel blockers*<br>  ○ *Amlodipine*<br>  ○ *Felodipine*<br>  ○ *Nifedipine*<br>  ○ *Nitrendipine*<br>• *Atrial natriuretic peptide*<br>• *L-Arginine* | • ***Furosemide***<br>• *Mannitol*<br>• *Endothelin receptor antagonist* |

*Taken from: Strategies to Reduce the Risk of Contrast-Induced Nephropathy: The CIN Consensus Working Panel*

**259. Answer is B (Use of High Osmolar Contrast Agents):** *Evidence-Based Practice of Critical Care: Expert Consult (Elsevier Health Sciences)2010/ 384,385; Strategies to Reduce the Risk of Contrast-Induced Nephropathy : The CIN Consensus Working Panel*
*(Link: http://www.nimbot.com/Med/Articles/RCIN/CIN%20Consensus%20Strategies.pdf)*

***Low Osmolar Contrast Media (LOCM) results in substantially less Contrast Induced Nephropathy (CIN) than High Osmolar Contrast Media (HOCM) in patients with preexisting renal dysfunction.***

The type of contrast medium used is an important risk factor for the development of contrast medium induced nephropathy with iso-osmolar contrast media (IOCM) and low-osmolar contrast media (LOCM) being less nephrotoxic than high-osmolar contrast agents in patients with pre-existing renal impairment. Therefore low-osmolar or iso-osmolar nonionic contrast media are recommended in high-risk patients to reduce the risk of contrast medium-induced nephropathy.

Note:
***No benefit has been demonstrated in those without renal dysfunction.***
*Although there is no proven decrease in CIN in normal populations, better tolerability and fewer side effects of LOCM have largely resulted in their supplanting HOCM in routine clinical practice.*

**260. Answer is A (Carcinoma of urinary bladder) :** *Bailey 23rd/1229*

*"Painless haematuria is by far the most common symptom and should be regarded as indicative of bladder carcinoma unless proven otherwise." - Bailey*
*The patient in question is **65 years of age and a smoker**, both factors being predisposition to bladder carcinomas and presenting with the most common symptom of **painless haematuria** thus almost deliniating the diagnosis.*

**Some facts about Bladder Carcinoma:**

- *Most common type of bladder carcinoma : Transitional cell carcinoma*
  *Most common type in areas where bilharzia is endemic - Pure Squamous cell*
  *Most common type arising from urachal remnant - Primary adenocarcinoma.*
- Predisposing factors that have been asked :

| | |
|---|---|
| Naphthylamine / Aniline dyes | Phenacetin exposure |
| Cigarettte smoking | Cyclophosphamide exposure |
| Bilharzia | Tyre, Rubber, cable and Dye industries |

- *Tumors of urothelium i.e. Pelvis, ureter and bladder are most commonly Transitional cell carcinomas.*
  ***But tumors of urethra are most commonly - squamous cell carcinomas.***

**261. Answer is C (Urine tumor markers)** : *Devita 6th/1397; Harrison 16th/579*

*Urine tumor markers are the single best answer of exclusion as these are neither sensitive nor specific enough to replace cystoscopy and cytology.*

- *'Individuals older than 40 years of age who develop haematuria , should have a **urine specimen for cytology and undergo cystoscopy and imaging of the urinary tract with an intravenous pyelogram or CT scan.**-Devita/Harrison*

**Recommended investigations in individuals greater than 40 years who develop haematuria include:** *Devita/H16th*
***Urinary cytology***$^{Q}$ for malignant cells
***Cystocopy***
***Imaging of the urinary tract with Intravenous Pyelogram or CT scan***$^{Q}$

- ***Other urine assay' (tumor markers)*** have been used to diagnose disease and follow up patients including flow cytometry, blood group antigens (Lewis x), cytokeratins, nuclear matrix proteins, Fibrin degradation products and telomerose. ***None is sensitive or specific enough to replace cystoscopy and urine cytology.*** *- Devita*

**262. Answer is D (Urine microscopy for malignant cytology)**: *Bailey & Love 24th/1463; Harrison 16th/539; Devita 6th/ 1397*

*Urine microscopy for malgnant cytology is the single best investigation amongst the options provided*

- Painless Gross Haematuria in a 60 year old smoker requires investigation to exclude carcinoma of the bladder.

**Recommended investigations in individuals greater than 40 years who develop haematuria include:** *Devita/H16th*
- ***Urinary cytology***$^{Q}$ for malignant cells
- ***Cystocopy***
- ***Imaging of the urinary tract with Intravenous Pyelogram or CT scan***$^{Q}$

***Amongst these recommended diagnostic procedures only 'urinary cytology for malignant cell's has been provided amongst the options and hence is the single best answer of choice.***

- **USG is not a recommended investigation for eliciting bladder tumours**

  USG by external, transrectal or transurethral route may define moderate size masses but it will not distinguish benign masses from solid masses. Also, it is unlikely to pick up small bladder tumours. *It has not been recommended as a first line investigation for eliciting bladder tumours.*
- **Routine Urine Microscopy and Plain X-Ray KUB will not give desired / sufficient information.**

**263. Answer is B (Renal Parenchymal Disease):** *Giai 7th/432; Nelson's 18th/1988; Manual of Endocrinology and Metabolism 4th/208; Hypertension Secrets (2002)/66; CPPT 19th/665*

***Renal Parenchymal Disease is the most common cause of hypertension in children and should be considered in the evaluation of all asymptomatic children with hypertension***

***Essential hypertension*** *is uncommon in children and accounts for only 5-10% of cases.* A diagnosis of essential hypertension in children should be considered only after excluding other secondary causes especially renal parenchymal disease. Absence of significant history and a normal urine examination does not exclude renal parenchymal as the cause

***Coarctation of Aorta*** *may present with hypertension in children but this is an uncommon cause* and usually presents with a charachteristic finging of blood pressure differential of > 10 mm Hg between upper and lower extremities, systolic hypertension in upper extremity along with decreased or absent femoral pulses

***Polycystic kidney Disease*** *does not usually present with hypertension in children.* Hypertension usually becomes clinically apparent in middle age and hence the condition is also called 'Adult' polycystic kidney disease.

**264. Answer is B (Pyeloplasty):** *Nelson's 18th/2237; 'Ultrasound of the Urogenital system' by Baxter & Sidhu 1st/92, 93; Essentials of Pediatric Urology 2nd/83, 84, 85, 86, 87; Campbell's Urology 8th/468; Textbook of Reconstructive Urological Surgery (2008) 1st/Chapter 16*

***The child in question is presenting with charachteristic feature of PUJ obstruction. He is a candidate for surgical management as differential function is only 19%. Open pyeloplasty (Anderson- Hynes dismembered pyeloplasty) is universally regarded as the gold standard operation of choice.***

**Ureteropelvic Junction Obstruction (UPJ Obstruction)**

- UPJ obstruction is the *most common obstructive lesion in childhood*[Q] and is the *most common cause of hydronephrosis found on prenatal and early postnatal ultrasonography*[Q].
- It is most commonly caused by intrinsic stenosis of a segment of ureter which is usually localized to the region of pelviureteric junction. Other causes include ureteric folds & extrinsic obstruction by crossing lower pole vessels.

**Presentation**

- ***Hydronephrosis*** revealed by maternal USG ***(Dilated renal pelvis but normal ureter)***
- Palpable Renal Mass in new borns or infants
- ***Abdominal flank or Back pain typically*** exacerbated by drinking large volumes of liquid
- UTI / Haematuria after minimal trauma

**Epidemiology**

- Left side more commonly involved than right (Bilateral = 10%)
- Male more commonly involved than females (M:F= 2:1)

**Initial Diagnosis by Ultrasonography**

- ***Hydronephrosis with dilated renal pelvis***
- Ureter if visualized is of normal caliber (not delated)

**Renal Differential function**

Nuclear Renography is used to determine Renal Differential function

- ***A differential function of <40% is considered significant and often an indication for surgical management***
- *Differential function of < 10% is often considered an arbitrary cut off for nephrectomy*

Management of PUJ

| Conservative | Surgical |
|---|---|
| Differential Renal function > 40% is usually managed conservatively especially when AP diameter of PUJ < 30 mm | • Differential Renal Function < 40% is usually an indication of surgical management especially if AP diameter of PUJ > 30 mm<br>• Deteriorating Renal function (a decrease in differential function by more than 10% on follow up USS).<br>• Persistant symptoms of pain, UTI<br>• Concern that the function of kidney will decline if it is left untreated (AP diameter of renal pelvis may indicate this). |

| Procedure of choice | Other procedures |
|---|---|
| ***Pyeloplasty is the surgical procedure of choice***<br>• ***Open pyeloplasty is considered the traditional gold standard***<br>• Laporascopic pyeloplasty is gaining growing acceptance | • External Drainage (Nephrostomy)<br>• Endopyelotomy<br>• Nephrectomy |

**External Drainage (Nephrostomy)**

This is used to provide temporary drainage particularly when children present with pyonephrosis or ***when differential renal function is <10-15%*** to assess potential recovery of function before considering definitive surgery.

**Endopyelotomy**

Endopyelotomy involves incising the UPJ junction by either a retrograde or antegrade route, by a minimally invasive approach. ***The success rate is inferior to open pyeloplasty. A large hydronephrosis and differential renal function <20% are considered relative contraindications for Endopyelotomy.***

**Nephrectomy**

Nephrectomy may be considered when renal differential function is very low and the likelihood of functionl recovery is minimal. ***Most pediatric urologists consider an arbitrary cut off for differential function in the range of 10-15%.*** However a reconstructive procedure (pyeloplasty) should always be considered as the procedure of choice to salvage the kidney.

**265. Answer is A (Diabetes mellitus):** *Harrisons 15th/1590 Fundamentals of diagnostic Radiology 3rd/885*

***Diabetes Mellitus is not associated with contracted (small) kidneys.***

*The kidneys are typically normal or increased in size in diabetic nephropathy – Harrisons*

Causes of Contracted Kidneys

- *Chronic Glomerulonephritis (Bilateral)*
- *Nephrosclerosis because of systemic hypertension (Bilateral)*
- *Chronic pyelonephritis (Usually unilateral)*
- *Global renal infarction (Unilateral)*
- *Radiation nephritis (Unilateral)*
- *Renal artery stenosis (Unilateral)*
- *Post obstructive atrophy (Unilateral)*

*Note that Acute Glomerulonephritis, and acute pyelonephritis are associated with enlarged kidneys but chronic cases are associated with contracted kidneys*

**266. Answer is C (Diabetes Mellitus):** *Refer Previous questions*

***The kidneys are typically normal or increased in size in diabetic nephropathy*** *- Harrison 14th / 1546, 15th/1590*

*Most forms of chronic renal insufficiencies lead to shrinkage or decrease in size of the kidney.*

*Notable exceptions, wherein kidney size is usually normal or increases include :*

1. Diabetic nephropathy ℮
2. Amyloidosis ℮
3. Polycystic kidney disease ℮

Kidney is contracted/shrunken in the remaining three conditions

- Benign nephrosclerosis ℮
- Chronic pyelonephritis ℮
- Chronic glomerulonephritis ℮

**267. Answer is D (Hepatitis) :** *Critical care Medicine 3rd/236 Rudolph Pediatrics 21st/1711*

***Chronic Active Hepatitis is a cause for distal type I Renal tubular acidosis which is associated with increased urinary loss of potassium.***

*"A high urinary K+ excretion with systemic acidosis is a charachteristic feature of renal tubular acidosis. Chronic Active Hepatitis is an established cause for distal renal tubular acidosis and may hence be associated with urinary $K^+$ excretion.*

**268. Answer is C (Glomerulonephritis):** *KDT 5th/717*

***Nephrotoxicity due to Amphoterecin B does not manifest as Glomerulonephritis.***

**Renal adverse effects of Amphotericin B :**

*Nephrotoxicity is the most important long term toxicity of Amphotericin B - KDT*

| Manifestations of Nephrotoxicity of Amphotericin B are : |
|---|
| - ***Azotemia*** |
| - ***Reduced G.F.R*** |
| - ***Acidosis (RTA)*** |
| - ***Hypokalemia*** |
| - ***Inability to concentrate*** *urine* |

*Nephrotoxity reverses slowly though often incompletely after stoppage of therapy.*

**269. Answer is C (FK 506):** *NICE Guidelines 'Immunosuppression therapy for renal transplantation in adults' (www.nice.org.uk/pdf/TA085 guidance.pdf) ; KDT 5th/790*

***The most common regimens include triple therapy with cyclosporine, azathioprine and prednisolone.***

***Immunosuppression has customarily constituted triple therapy with : (NICE Guidelines)***

1. *A calcineurin inhibitor (cyclosporin);*
2. *An antiproliferative agent (azathioprine); and*
3. *A corticosteroid (prednisolone)*

*However, a small number of treatment centers use a policy of initial monotherapy with a calcineurin inhibitor, adding in other agents if necessary.*

**Immunosuppressive therapy for renal transplantation in adults**

**Induction therapy**

- Is a course of intensive immunosuppressive for about 2 weeks immediately post operatively (though often started immediately pre-operatively) with the aim of 'switching off' the immune system after transplantation to reduce the likelihood of accelerated rejection and acute rejection.
- It has also been used as a means of reducing exposure to calcineurin inhibitors in the early stages after transplantation when the graft may be particularly vulnerable to their nephrotoxic effects.
- The term induction therapy has usually been linked with the use of the following agents:
  - The polyclonal antibodies antithymocyte immunoglobulin (ATG)
  - The antilymphocyte immunoglobulin (ALG), and
  - The monoclonal antibody muromonab-CD3 (OKT3)

**Initial therapy**

- Is the treatment given to all recipients (except where the donor is an identical twin) for 0-3 months after transplantation.
- Initial therapy is usually 'triple therapy', in which a clacineurin inhibitor (traditionally cyclosporine) is used as the 'primary agent' in combination with a corticosteroid (prednisolone) and azathioprine.
- Occasionally, dual therapy (cyclosporine plus costicositeroid) is used.

**Maintenance therapy**

- Is the treatment that patients receive long-term, throughout the duration of allograft survival
- Maintenance therapy is often identical to initial therapy (triple therapy) but at a reduced dosage because the transplanted kidney becomes immunologically more stable with increasing time.
- However, agents used in maintenance therapy may be altered in response to
  - Development of acute rejection, severe infections or toxicity.
  - Poor tolerability leading to non-adherence

**270. Answer is B (Sterile Pyuria):** *Textbook of Pulmonary and Critical Care Medicine (JP), 2011/632; Oxford Desk Reference: Nephrology (Oxford University Press), 2009/256; Oxford Textbook of Medicine 4th/563*

***The most common clinical presentation of Urological Tuberculosis is Sterile Pyuria.***

*'The most common clinical presentation of urological tuberculosis is sterile pyuria and painless hematuria'*
*- Textbook of Pulmonary and Critical Care Medicine*

*'Renal Tuberculosis is probably underdiagnosed because it is frequently asymptomatic Many cases are diagnosed as a result of routine detection of sterile pyuria. The development of symptoms reflects a more advanced stage of disease'*
*- Oxford Textbook of Medicine*

**Classical Renal Tuberculosis**

| Early Clinical Features: | Late Clinical Features: |
|---|---|
| • Symptoms of cystitis;<br>• Microscopic or macroscopic hematuria;<br>• Pyuria with negative bacterial culture ('sterile pyuria');<br>• Constitutional symptoms. | • Nephrolithiasis and ureteral colic;<br>• Intractable frequency and urgency;<br>• Refractory hypertension;<br>• Renal insufficiency due to obstructive nephropathy. |

*****

# Gastrointestinal System

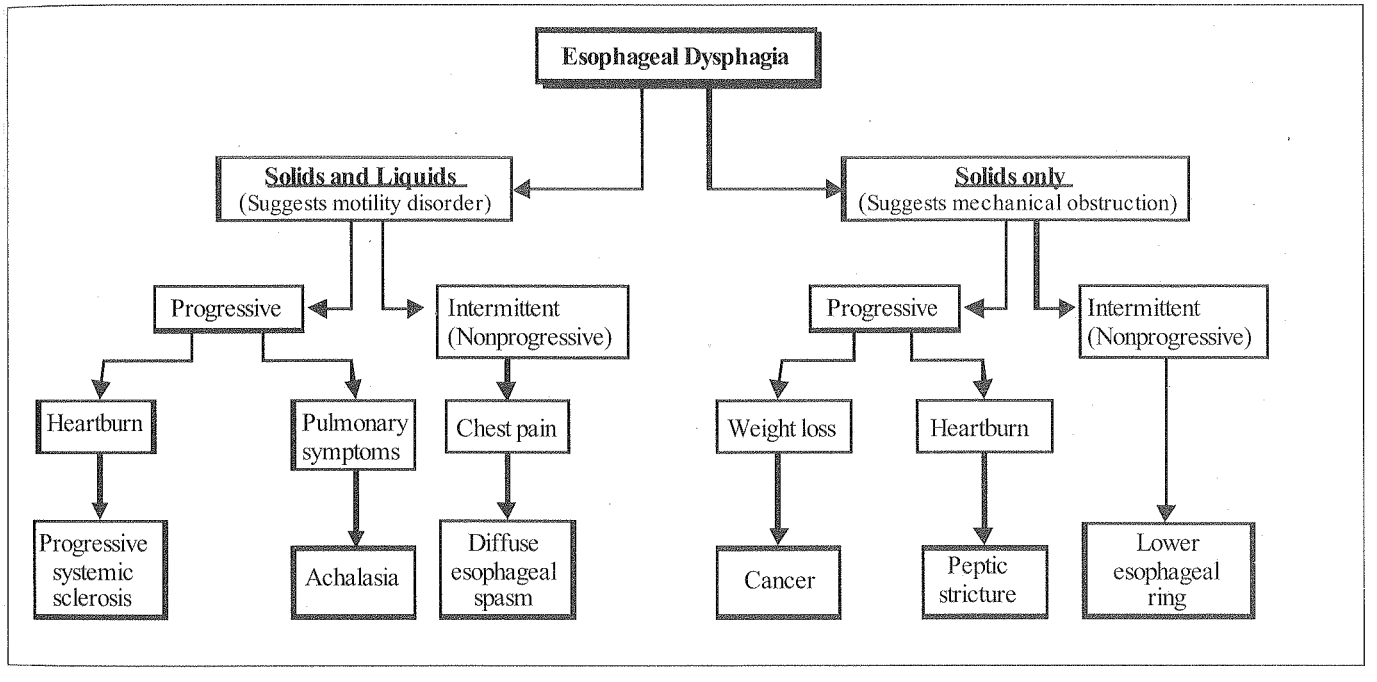
## ESSENTIAL REVISION NOTES

### Esophageal Conditions

#### Dysphagia (General / Differential Diagnosis):

**Esophageal Dysphagia**

| Progressive | Intermittent |
|---|---|
| • *Achalasia* | • *Lower esophageal ring/Shatzki ring* |
| • *Progressive systemic sclerosis* | • *Diffuse esophageal spasm* |
| • *Peptic stricture* | • *Zenker's diverticulum* |
| • *Carcinoma* | |




- **Achlasia Cardia** is associated with *Progressive dysphagia* to *both solids and liquids*
  *Rat-tail esophagus with a dilated proximal esophagus and narrow lower end suggests a diagnosis of Achlasia cardia. (Dhingra 4th/305)*
- **Esophageal carcinomas** are associated with *progressive dysphagia*. Dysphagia is *initially only for solids* at presentation (may prgress to cause dysphagia to liquids also)
  *Narrow and irregular esophageal lumen suggests a diagnosis of esophageal carcinoma (Dhingra 4th/306)*
- **GERD** is asociated with *progressive dysphagia* to *solids alone* at presentation.
  *Stricture or ulcer in the esophagus suggests a diagnosis of Gastrophageal Reflux disease (GERD)*
- **Diffuse esophageal spasm** is associated with non-progressive dysphagia to both solids and liquids.
  *The charachteristic barium swallow findings in diffuse esophageal spasm is the corkscrew esophagus (appearance of curling or multiple ripples in the wall, sacculations and pseudodiverticula)*
- **Lower esophageal rings (Schatzki's ring)** *is associated with Non- progressive (episodic) dysphagia only for solids. The ring is apparent as a constriction in the lower esophagus on barium swallow.*

## Investigations for Esophageal Dysphagia

Esophageal Dysphagia

*Initial investigation should be Barium swallow*[Q]

| Dysphagia for both liquids & solids | Dysphagia for solids alone |
|---|---|
| Suggests esophageal motility disorder<br>- *Achalasia*<br>- *Diffuse Esophageal spasm* | Suggests mechanical obstruction<br>- *Carcinoma*<br>- *Stricture*<br>- *Web* |
| ↓ | ↓ |
| ***Investigation of choice is Manometry*** | ***Investigation of choice is endoscopy*** |

- *Barium swallow is the recommended initial investigation for a case of Esophageal Dysphagia*
  *'In evaluating a patient with dysphagia, a barium swallow should be the first test performed'-Current Otorhinology 2nd/488*
- *Endoscopy is the investigation of choice for dysphagia from mechanical obstruction*
- *Manometry is the investigation of choice for dysphagia from esophageal motility disorders*

**Dysphagia Lusoria**

*Dysphagia Lusoria refers to dysphagia arising from symptomatic compression of the esophagus by an aberrant blood vessel.*

## Types of Contractions seen in Esophagus

Three types of Contractions are seen in Esophagus

| Primary Contractions (Primary Peristalsis) | Secondary Contractions (Secondary Peristalsis) | Tertiary Contractions (Tertiary Peristalsis) |
|---|---|---|
| • *Progressive contractions* | • *Progressive contractions* | • ***Non progressive contractions*** |
| • Triggered by voluntary swallowing | • Triggered by distension or irritation of esophagus (but not by voluntary swallowing) | • Occur spontaneously and simultaneously between swallows |

***Simultaneous, Non progressive, Non Peristaltic waves are called Tertiary contractions***

# Achalasia Cardia

## Achalasia Cardia (Primary esophageal motility disorder)

### Physiological Characteristic

- Absence of esophageal peristalsis
- Increased pressure of LES
- Failure of LES to relax in response to swallowing

### Pathogenesis

- True etiology unknown
- Degeneration of Myenteric plexus of Aurerbach's with loss of postganglionic inhibitory neurons is noted (These neurons contain NO and VIP which mediate LEs relaxation)
- Sparing of postganglionic cholinergic fibres
  (Increased Les resting pressure and insufficient relaxation)

### Presentation

- Dysphagia is the most common symptom
  Dysphagia is present for both solids and liquids and is progressive
- Regurgitation is the second most common symptom
- Chest pain may also occur

### Investigations

- *Esophageal Manometry is the key test in establishing the diagnosis*

| Physiological /Manometric features of Achalasia |
|---|
| •*Elevated Resting pressure of LES (>45 mmHg)*Q |
| •*Incomplete LES relaxation (in response to swallowing)* Q |
| •*Absence of distal esophageal peristalsis* Q |

- *Barium swallow should be the initial test performed*

| Diagnosis suggested by: |
|---|
| •*Dilated sigmoid oesophagus* |
| •*Persistant beak like narrowing of distal oesophagus* |

### Complications

- *Achalasia is a risk factor for Esophageal carcinomaQ*
- Achalasia predisposes to squamous cell carcinomaQ

### Treatment

*Surgical Treatment*

- *Laparoscopic Heller's myotomyQ and partial fundoplication is the procedure of choice*
  Esophagectomy is not used in the treatment

*Non surgical treatment* includes medications that reduces LES pressure

- Intrasphinteric injection of botulinum toxin and/or
- Pneumatic dilatation

# Diffuse Esophageal Spasm

Diffuse Esophageal spasm (Corkscrew esophagus)

Diffuse Esophageal spasm is a poorly understood hypermotility disorder of the oesophagus

Presentation

- The clinical presentation is typically that of *Chest pain and Dysphagia*
- ***'The most common symptom is intermittent chest pain***$^{Q}$ (>dysphagia)
- Chest pain mimics angina or pain of coronary artery disease
  - *Squeezing pressure in the chest that may radiate to the Jaw, arms or upper back*
  - *Symptoms are aggravated by emotional stress, exertion (or related to eating)*

*Chest pain*$^{Q}$
*Dysphagia*$^{Q}$

Diagnosis

***Manometry is the key to establish the diagnosis***
*The diagnosis is usually made by an esophagogram (Barium swallow) and monometric study*
*Ambulatory pH monitoring should be performed to rule out abnormal reflux*

Esophagogram
(Barium Swallow)

- *Corkscrew esophagus*$^{Q}$ is *classical of Diffuse esophageal* spasm (seen in about 30% of cases)

(Radiological evidence of tertiary contractions)

Manometry

- ***Manometry is the key to establish the diagnosis (CSDT)***
  *Correlation of subjective complains with evidence of spasm (induced by vagomimetic drug bethenechol) on manometric studies prvide convincing evidence-* Sabiston
- *Esophageal monometry is the only test that distinguishes diffuse esophageal spasm from other primary esophageal motor disorders* - CSDT
- *An ambulatory motility record (ambulatory manometry) is preferred over standard manometry* as contractions are intermittent and normal peristalsis is seen in between. *Ambulatory manometry is the single best investigation with a sensitivity of 90% and specificity of 100%*

| Ambulatory 24 hour pH monitoring |
| --- |
| *Gastro esophageal reflux disease may mimic diffuse esophageals spasm Ambulatory pH monitoring must be performed to rule out abnormal reflux which is the most common cause of non cardiac chest pain* |

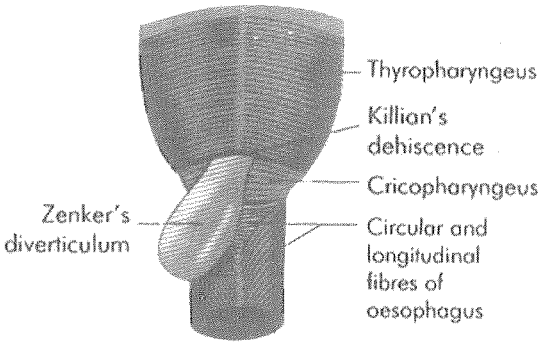
***Diffuse esophageal spasm is synonymous with 'corkscrew esophagus' or Rosary esophagus*** **- Bailey**
*In diffuse esophageal spasm, barium swallow shows that normal sequential peristalsis below the aortic arch is replaced by uncoordinated simultaneous contractions that produce the appearance of curling or multiple ripples in the wall, sacculations, and pseudodiverticula- the "corkscrew" esophagus.*

# Zenker's Diverticulum

**What it is :**

It is a *pulsion diverticulum*[Q], where pharyngeal *mucosa*[Q] herniates *through the Killihan's dehiscence*[Q] (a weak area *between two parts of Inferior Constrictor*[Q]). **(Zenker's Diverticulum occurs in the pharynx and not in the esophagus)**

- Zenker's diverticulum originates from the *posterior wall* of the pharynx through the killian's dehiscence
- Killian's dehiscence is a weak area between
  - Oblique fibres of the Thyropharyngeus (part of inferior constrictor muscle) superiorly
  - Transverse fibres of the cricopharyngeus (part of the inferior constrictor muscle) inferiorly
- Herniation *starts in the midline posteriorly*, however as the out pouching enlarges, it localizes to one side of the oesophagus most commonly on the left side.




Hypopharyngeal (Zenker's) diverticulum.

Hypopharyngeal mucosa herniates through the Killian's dehiscence a weak area between two parts of inferior constrictor

- **Zenker's diverticulum is an acquired diverticulum and not a congenital diverticulum**
  These are *acquired pulsion diverticulae* that usually occur in people older than 60 years as their pharyngeal muscle tone and elasticity decreases.
- **Zenker's diverticulae are false diverticulae**
  Zenker's diverticulum *is a false diverticulum* because it does not contain all the anatomic layers of the esophageal wall Zenker's diverticulum involves protrusion of *only the mucosa (and submucosa)* through the posterior muscle layers

**Age of presentation**

This condition is usually seen after 60 years of age (*elderly*) [Q]

**Symptomatology / presentation**

- ***Dysphagia***[Q] : As mouth of the sac is wider than the opening of esophagus, food preferentially enter the sac. When the pouch gets filled with food, it presses on the esophagus & produces ***Dysphagia***. [Q]
- ***Gurgling Sound***[Q] is produced during swallowing.
- ***Halitosis*** or foul smell is frequently associated
- ***Cough & Aspiration pneumonia***[Q] : food eaten *over the last few days*[Q] may regurgitate as it collects in the pouch causing cough and aspiration pneumonia.
- ***Malnutrition***[Q] : Patient is often malnourished due to dysphagia.

> *The most frequent complications of Zenker diverticulum is 'aspiration' into the tracheobronchial tree which can in turn present with pneumonia and Lung Abscess.*

***Investigations***

- Barium swallow is the diagnostic procedure of choice for Zenker's diverticulum
  Zenker's diverticulum are often identified by Lateral x-rays on Barium swallow

**Treatment**

- *Simple Excision of pouch*
- *Excision of pouch and cricopharyngeal myotomy* [Q]
- *Dahlman's procedure*[Q] : Done in poor-risk debilitated patients. The partition wall between esophagus and pouch is divided by diathermy.

## Oesophageal Ring

***Schatzki ring is a mucosal / submucosal ring at the squamo-columnar junction of distal esophagus that may present with intermittent dysphagia.***

**Schatzki Ring (Oesophageal Ring)**

- *It is a characteristic short segment of luminal stenosis*
- ***Occurs in the lower esophageal at the gastroesophageal junction (squamo-columnar junction)***
- ***It is made up only of mucosa and submucosa and narrows the lumen only to a few millimeters.***
- *True aetiopathogenesis is not known*
- *Usually asymptomatic*
- ***Most common presentation intermittent dysphagia only for solids.***
- *Often associated with a hiatus hernia.*
- *Frequently leads to incorrect diagnosis of diffuse esophageal spasm*
- *Treatment involves esophageal dilatation or endoscopic diathermy/laser.*

## Oesophageal Web (In association with Plummer Vinson Syndrome)

*Plummer Vinson syndrome refers to the combination of hypopharyngeal webs and iron deficiency anemia in middle aged women*

**Plummer Vinson Syndrome (Patterson Kelly)**

- *Upper esophageal web*
- *Iron deficiency anemia*
- *Koilonychia*
- *Glossitis and angular stomatitis*

## Mallory Weiss Syndrome:

***Mallory-Weiss Syndrome is associated with a tear of the gastric mucosa near the squamocolumnar mucosal junction***

Mucosal Tear (Mallory-Weiss Syndrome)

- The tear usually involves the gastric mucosa near the squamocolumnar mucosal junction near cardia
- This tear is usually caused by vomiting, retching, or vigorous coughing.
- The tear is usually linear.
- Patients present with upper gastrointestinal bleeding ***(Hemetemesis)***
- Association with alcoholism and hiatus hernia
- In most patients, bleeding ceases spontaneously

(Continued bleeding may respond to vasopressin therapy or angiographic embolization. Surgery is rarely needed)

# Barret's Esophagus

## Barret's Esophagus

- *Barret's esophagus is a metaplasia of the esophageal mucosa caused by replacement of squamous epithelium with columnar epithelium.*
  *Specialized intestinal epithelium (intestinal metaplasia) is the most common and most important type of columnar epithelium seen in Barret's esophagus.*

**Barret's esophagus (columnar metaplasia)**

**Metaplasia of squamous epithelium into columnar epithelium**

↓

**Three types of Columnar Epithelium may be seen**

| Gastric Type | Junctional Type | Intestinal Type |
|---|---|---|
| *Morphologically indistinguishable from normal gastric epethelia* | *Morphologically indistinguishable from normal gastric epethelia* | *Morphologically distinct and readily distinguishable from gastric epethelia*<br>• This is the most common type<br>• Most commonly associated with dysplasia & carcinoma |

- *Metaplasia characteristically affects the distal (lower) oesophagus*[Q]
- *It is consequence of severe reflex esophagitis*[Q]

***Epidemiology***

- *More common in men*[Q] *(Males > Females)*
- *More common in whites*[Q] *(Whites > Blacks)*
- *More common with increasing age*[Q] *(incidence increases with age)*

***Complications***

- *Peptic Ulcer (Barret's Ulcer: Chronic Peptic Ulceration in the columnar lined mucosa)*
- *Strictures (Can lead to high (midoesophageal) and long strictures)*
- ***Considered a premalignant condition***[Q]
  *Type of cancer associated in an adenocarcinoma*[Q] *(Dysplagia – cancer sequence)*
  *Columnar metaplasia that carries maximum risk of adenocarcinoma is intestinal metaplasia (intestinal epithelium)* [Q]

**Diagnosis**

- **Diagnosis can be suggested by Endoscopy**
  *Endoscopy shows a 'salmon pink' epithelium above the gastroesophageal junction which replaces the whitish squamous epithelium.*

- **Diagnosis is confirmed by biopsy**
  *Diagnosis is confirmed by pathological examination and requires the identification of columnar (intestinal) type epithelium characterized by the presence of goblet cells.*

**Treatment**

- *Barret's metaplasia once established does not regress with conservative management*
- *Although medical treatment does not regress the metaplastic changes, it is still advocated to prevent continued insult*

# Esophageal Carcinoma

## Histological Variants of Esophageal Carcinoma

- ***By far the most common esophageal cancer world wide is squamous cell carcinoma*** *(Prevalence)*
- *Most prevalent esophageal cancer world-wide (old + new cases) is squamous cell ca*
- *Most common esophageal cancer world-wide (new cases) is Adenocarcinoma*
- ***Most common esophageal cancer in India is Squamous cell Carcinoma***

## Site of Esophageal Carcinoma

- ***The lower third of the esophagus is the most common site of esophageal cancer and accounts for about 50% of all esophageal cancers.***

| Site of esophageal cancer (All histological types) | % of total |
|---|---|
| Upper 1/3rd | 15% |
| Middle 1/3rd | 35% |
| ***Lower 1/3rd*** | ***50%*** |

- ***Most common site of Esophageal carcinoma in India is middle one third of the esophagus***
  *Eighty to ninety percent of esophageal cancers in India are squamous cell carcinomas, and the most common site is middle 1/3rd of esophagus*

**Site of Esophageal Carcinoma based on histological type**

- ***The most common site of squamous cell (histological subtype) is middle 1/3 of esophagusQ***
- ***The most common site of adenocarcinoma (histological subtype) is lower 1/3rd of esophagusQ.***
  *Esophageal Adenocarcinoma invariably arises from Barret's esophagus (Barret's ulcer) which is characteristically located in the distal esophagus around the gastroesophageal junction*

## Epidemiology

- ***Men > Women (≈4 : 1) (More common in Men)***
- ***Predominantly*** *affects older age group (> 50 years)*

**Predisposing factors for carcinoma esophagus :**

1. ***Alcohol consumption*** Q
2. ***Smoking cigarettes*** Q
3. **Ingested Carcinogens**
   - *Nitrates* Q
   - Smoked opiates
   - Fungal toxins in pickled vegetables
4. **Mucosal damage**
   - ***Chronic Achalasia*** Q
   - Lye ingestion / Hot tea
   - Radiation induced strictures Q
5. **Host Susceptibility**
   1. *Patterson Kelley syndrome* Q *or* ***Plummer Vinson syndrome*** Q
      *Esophageal web* Q *+ Glossitis* Q *+ Iron deficiency* Q
   2. ***Tylosis palmaris et plantaris*** Q *: Congenital hyperkeratosis* Q *and pitting of palms and soles* Q
6. *Chronic Gastric Reflux, ie. Barrett's esophagus for Adenocarcinoma* Q

**Risk factors for Esophageal Adenocarcinoma**

- ***Barrets esophagus***
- *Gastroesophageal Reflux Disease (GERD)*
- ***Scleroderma***
- *Smoking*
- *Alcohol*
- *History of colon cancer*
- *Medications : Long term use (> 5 years) of Theophylline & β agonists.*

## Presentation

**Dysphagia is the most common symptom**

*Esophageal carcinomas* are associated with *progressive dysphagia.* Dysphagia is *initially only for solids* at presentation (may prgress to cause dysphagia to liquids also)

## Investigation

*Investigation of choice is Endoscopy*

## Treatment

- ***Chemotherapy for esophageal cancer has improved considerably with the advent of regimens containing Cisplatin.***
  *The best responses are seen in Squamous cell carcinomas*
- *Surgical Treatment involves complete Esophagectomy*
  *Stomach appears to be the 'conduit' of choice after partial or complete Esophagectomy because of ease in mobilization and its ample vascular supply*

## Stomach and Duodenum

# Peptic Ulcer Disease & H. Pylori Infection

**Aetiological Factors in peptic ulceration:**

**Aetiological Factors in peptic ulceration**

| Primary Aetiologcial Factors (selected) | Associated Factors / Conditions (selected) |
|---|---|
| • *H. pylori infection*<br>• *NSAID's and other drugs eg. steroids*<br>• *Stress – Head injury / Burns*<br>• *Bile Reflux*<br>• *Smoking / Alcohol use*<br>• *Genetic Factors* | • *Endocrinal Disorders*<br>- *MEN*<br>- ***Primary Hyperparathyroidism***<br>- ***Zollinger Ellison Syndrome***$^{Q}$<br>- *Cushing's syndrome*<br>• ***Cirrhosis***$^{Q}$<br>• *Chronic Renal Failure*<br>• *Chronic Pulmonary Disease*<br>• *Chronic Paracreatic Disease*<br>• *Alpha 1 Antitrypsin deficiency* |

**Aetiological factors in Gastric Ulcers vs Duodenal Ulcers:**

| Causal factor | Gastric ulcer | Duodenal ulcer |
|---|---|---|
| **Hellicobacter pylori** | Important | Very important |
| **NSAIDs and aspirin** | Important | Important |
| **Acid** | ***Normal or low acid output*** | ***High or normal acid output*** |
| **Bile reflux** | Important | Unimportant |
| **Smoking** | Important | Important |
| **Stress** | Evidence for head injuries and burns only | |
| **Family history** | Uncommon | Common |

***Gastric ulcers are associated with normal or decreased gastric acid output. High Acid output is a feature of Duodenal Ulcers.***

## H.pylori Infection

- H. Pylori is a gram negative, spiral, flagellated bacillus
- H. Pylori *infection is more prevalent in developing countries.*
  *The prevalence of H. pylori is approx. 30% in U.S. and other developed countries as against > 80% in most developing countries. The chances of reinfection are also high in developing countries*
- H. Pylori eradication decreases the likelihood of occurrence of complications and recurrence

### Diseases associated with H. Pylori infection:

| Diseases associated with H. Pylori infection |
|---|
| 1. *Duodenal ulcer* |
| 2. *Gastric ulcer* |
| 3. *Chronic superficial gastritis* |
| 4. *Chronic atrophic gastritis* |
| 5. *Gastric adenocarcinoma* |
| 6. *Lymphoproliferative disease (MALT)* |
| 7. *Gastroesophageal reflux disease* |

*MALT stands for Mucosa Associated Lymphoid Tissue Lymphoma*

### Gastritis associated with H. Pylori Infection:

#### Gastritis due to H. pylori infection is predominantly antral

*Antral gastritis is associated with DU formation.*

#### Gastritis involving the corpus is also seen

*This predisposes to development of gastric ulcer, gastric atrophy and ultimately gastric carcinoma.*

| *Antral predominant gastritis* | *Corpus Predominant atrophic gastritis* | *Non atrophic pangastritis (chronic superficial gastritis)* |
|---|---|---|
| Duodenal ulcer | Gastric ulcer<br>Gastric adenocarcinoma | MALT Lymphoma |

### Diagnostic tests used for H pylori:

| Invasive | Non invasive |
|---|---|
| *1. Endoscopy based Biopsy Urease test* | *1. Urea breath tests :* |
| • Here specimen from antral biopsy are tested for "Urease".<br>• It is the most convenient endoscopy based test.<br>• It is *quick*$^{Q}$ and *simple*$^{Q}$ however it is neither fully sensitive nor fully specific | • Here patient drinks a labelled urea solution and blows into a tube.<br>• If H. Pylori urease is present, the urea is hydrolysed and labelled carbondioxide is detected in breath samples<br>• It is thus a simple, safe test and cheaper than endoscopy |
| *2. Histology :* | *2. Serological :* |
| Here the biopsy specimen is subjected to histological examination.<br>It is *accurate*$^{Q}$, but time consuming | • Here specific IgG levels in serum are assessed.<br>• Does not differentiate between active and remote infection.<br>• Nevertheless it is particularly suited as an *epidemiological tool* |
| *3. Culture :* | *3. Stool antigen test :* |
| • Here the biopsy specimen is put in a culture medium.<br>• This is accurate $^{Q}$, and permits determination of antibiotic susceptiblities, but is also time consuming. | • New test appears less accurate than urea breath test<br>• Useful for follow up after treatment |

***Diagnostic Tests for Helicobacter pylori*** – *Harrison*

| Test | Sensitivity | Comments |
|---|---|---|
| Serology | 95 | Does not differentiate between active and remote infection; epidemiologic tool; titer decreases slowly after eradication |
| Urease assay | | |
| Breath | 90-95 | Simple ; may be used to monitor therapy |
| Biopsy | 90-98 | Requires endoscopy |
| Histology | | Requires endoscopy; may be essential if antibiotic resistance emerges |
| Culture | 70-95 | Requires endoscopy; may be essential if antibiotic resistance emerges |

*ELISA (An enzyme linked immuno-sorbant assay) is the most commonly used serological method.*
*ELISA has proved to be sensitive and specific and is* ***particularly suited for Epidemiological studies***
*Urease breath test (Non Invasive Test) is the test of choice for documenting eradication is.*
*Urease breath test detects H. pylori infection by 'bacterial urease activity' and remains positive till the bacteria have not been eradicated with treatment. Thus urease breath test becomes negative only after eradication of organism following treatment and not with chronic infection.*

***Assessing success of Treatment / Eradicatiion of H. Pyrlori :***

- Assessment should be done atleast 4 weeks after completin of anti H. Pylori therapy.
- In the assessment of treatment success non-invasive tests are normally preferred. – Harrison

**Assessment of success of treatment**

| Non invasive tests are preferred | Inasive tests are not preferred |
|---|---|
| **Urea breath test** : ***Test of choice for documenting eradication.*** | **Biopsy based tests** (Biopsy Urease test, Histology / Culture) *are invasive tests based on Endoscopic biopsy.* |
| **Stool antigen test** : *If UBT is not available a stool antigen test should be considered for documenting eradication* | ***These may be used to document eradication but are not preferred for this purpose.*** |
| **Serological testing** : Is **not useful for purpose of documentation of eradication** as antibody titres fall slowly and often do not become undetectable | |

## Treatment of H.Pylori Infection

| Indications of Treatment : |
|---|
| H-Pylori related duodenal and gastric ulceration |
| Low grade B cell MALT Lymphoma |

*H.pylori should be eradicated.*

## Recommended Regimens for Eradication of H.Pylori

| Recommended Regimens for Eradication of H. Pylori *(Harrison)* |
|---|
| **TRIPLE THERAPY** |
| 1. Bismuth subsalicylate plus Metronidazole plus Tetracycline |
| 2. Ranitidine bismuth citrate plus Tetracycline plus Clarithromycin or Metronidazole |
| 3. PPI plus Clarithromycin plus Metronidazole or Amoxicillin |
| **QUADRUPLE THERAPY** |
| PPI plus Bismuth subsalicylate plus Metronidazole plus Tetracycline |

*All PPI (*Omeprazole (20mg), Lansaprazole (30mg) *Rabeprazole (20 mg), Pantaprazole (40 mg),) are given twice daily except Esmeprazole (40 mg once daily)*

**The most successful are the Triple and Quadruple multi-drug regimens:**

| Name | Drug 1 | Drug 2 | Drug 3 | Drug 4 |
|---|---|---|---|---|
| OCA | Omeprazole (20 mg BD) | Clarithromycin (500 mg BD) | Amoxicillin (1g BD) | |
| OCM | Omeprazole (20 mg BD) | Clarithromycin (500 mg BD) | Metronidazole (500 mg BD) | |
| OBTM | Omeprazole (20 mg BD) | Bismuth Subsalicylate (2 tabs QID) | Tetracycline (500 mg QID) | Metronidazole |

## Peptic Ulcers: Gastric Ulcers and Duodenal Ulcers

- ***The most common site for peptic ulceration is the First part of duodenum***

| Sites in order of decreasing frequency : |
|---|
| *1. Duodenum, 1st portion* Q |
| *2. Stomach, usually antrum* Q |
| *3. At the gastro-esophageal junction, in the setting of gastroesophageal reflux* Q |
| *4. Within the margins of a gastrojejunostomy* Q |
| *5. In the duodenum, stomoch or jejunum of patients with Zollinger- Ellison Syndrome* Q |
| *6. Within or adjacent to a Meckels diverticulum that contains ectopic gastric mucosa* Q |

- ***The most common site of gastric ulcers (benign) is on the lesser curvature straddling the incisura angularis.***
- ***The most common complication of both acute and chronic peptic ulcers is gastrointestinal haemorrhage.***
- ***The most common arterial source of a hemorrhage in duodenal ulcers is the gastroduodenal artery.***
- ***Highly selective vagotomy is the procedure of choice for the management of chronic duodenal ulcers, except in situations where ulcer recurrence rates are high.***

**Highly selective vagotomy:**

- In highly selective vagotomy nerves of Latarjet supplying the antrum are preserved. Q
- A drainage procedure is not required Q
- Operation mortality is lower than in any other definitive operation for duodenal ulceration. Q

- ***Vagotomy with Antrectomy is associated with lowest recurrence rates.***

Operations for duodenal ulcers:

| Operation/Procedure | Mortality | Recurrence rate (%) | Comments |
|---|---|---|---|
| Vagotomy and drainage | Intermediate | Intermediate | Selectively used |
| Highly selective vagotomy | Low (minimum) | ***High*** | Procedure of choice as it has the least complication rate |
| Vagotomy and antrectomy | *High* | ***Low (minimum)*** | Procedure with least recurrence rate.<br>Procedure of choice when recurrence is the major problem |

| Operation with maximum reduction in acid production | Operation with minimum operative mortality | The most widely used procedure in India |
|---|---|---|
| Truncal vagotomy and antrectomy | Highly selective vagotomy | Truncal vagotomy plus a drainage procedure<br>*Gastrojejunostomy is at present the most widely used procedure.* |

### Stress ulcers

- *Stress ulcers after head trauma : Cushing's Ulcers*
- *Stress ulcers after severe burns : Curling's Ulcers*

**Cushings ulcers** :
Are acute ulcers of the upper GI tract associated with intracranial injury or an *increase in intracranial pressure.*

| These ulcers my involve the |
|---|
| *Stomach* Q |
| *Proximal duodenum* Q |
| *Esophagus* Q |

**Complication** : Haemorrhage and perforation Q
**Treatment:** Correction of increased intracranial pressure + usual treatment of acute erosions and ulceration.

## Pyloric Stenosis : Gastric Outlet Obstruction

**Pyloric Stenosis**

- Pyloric Stenosis refers to Gastric Outlet Obstruction, classically resulting from hypertrophy of musculature of the pylorus adjacent to the antrum.
- Gastric outlet obstruction in a patient with peptic ulcer disease usually suggests pyloric stenosis.
- Commonly the stenosis is found in the first part of the duodenum, the most common site for a peptic ulcer. (The *term pyloric stenosis may be a misnomer as the stenosis is seldom at the pylorus)*

**Epidemiology**

- First born male child is characteristically most commonly affected
- It is four times more common in males as in females
- The condition does not present at birth. It is most commonly seen 4 weeks after birth

**Presentation**

- Vomiting is the presenting symptom (child vomits milk and *no bile is present*[Q])
  *The vomiting of hydrochloric acid results in hypochloremia and alkalosis i.e. hypochloremic alkalosis*[Q]
  ***Metabolic alkalosis with paradoxical aciduria is typical***
- ***Immediately after vomiting the child is hungry i.e. loss of appetite does not occur.***
- Weight loss is striking and rapidly the infant becomes emaciated and dehydrated.
  However, greater awareness of pyloric stenosis has led to earlier identification of patients and hence with ***fewer incidences of chronic malnutrition and severe dehydration*** - *Nelson 10th/1130*

Diagnosis

- The diagnosis is usually made with a test feed : In this the baby is fed with the bottle by a nurse or mother and surgeon : palpates the abdomen with a warm hand to detect the lump and observes the characteristic peristatic waves pass across the upper abdomen.
- Ultrasonography is the investigation of choice
- Pathologically musculature of pylorus adjacent to antrum is grossly hypertrophied

Treatment

- Hyperchloremic alkalosis is common and following diagnosis first concern is to correct metabolic abnormalities - child is rehydrated with dextrose saline & potassium[Q]
- Treatment *of choice : Ramsted's operation - 'Pyloromyotomy'*

## Dumping Syndromes

**DUMPING SYNDROMES: POST-CIBAL SYNDROMES**

**DUMPING SYNDROME** refers to a syndrome of abdominal and vasomator symptoms which results from dumping of food stuffs with a high osmotic load, from the stomach, into the small bowel.

**TYPES OF DUMPING SYNDROMES**

Dumping Syndrome is actually of two types:

- **Early dumping syndrome** : *Loss of storage capacity of stomach and ablation, by pass or destruction of pylorus, results in rapid emptying of hyperosmolar chyme into duodenummm and small intestine*. Extracellular fluid then shifts into the intestinal lumen to restore isotonicity resulting in decreased intravascular volume, which gives rise to the vasomotor symptoms.
- **Late dumping syndrome:** This is *Reactive hypoglycemia*[Q]. The carbohydrate load in thesmall intestine later causes a rise in plasma glucose, which in turn causes insulin levels to rise causing a secondary hypoglycemia.

**TREATMENT OF DUMPING SYNDROMES**

- Both types of postcibal syndrome are treated by dietary measures including:
  - Limitation of sugar containing liquids and solids,
  - Elimination of liquids at meal time, and
  - Eating of frequent small meals.
- In severe cases, symptoms may improve, with the somatostatin-analogue *Octreotide*.

***There is no role of surgery in management of post cibal syndromes.***

# Menetrier's disease

*Menetrier's disease is characterized by hypertrophy of gastric mucosa and not by exophytic growth.*

## Menetrier's disease

Menetrier's disease is a relatively rare disorder of the stomach characterized by large tortuous mucosal folds

## Etiology

- Etiology is unknown
- Over expression of growth factors such as TGF are suggested

## Pathology

Gross

- Marked Hypertrophy of gastric folds/Rugae♀
- Hypertrophy results from hyperplasia of mucus producing cells (mucosa)♀
- Hypertrophy is most prominent in the body and fundus ♀

Histological/microscopic

- Massive foveolar hyperplasia (Hyperplasia of surface and glandular mucosal cells).
- Pits of gastric glands elongate and may become tortuous
- Lamina propria may contain a mild chronic inflammatory infiltrate
  (Note: Although lamina propria may contain an inflammatory infiltrates, Menetrier's disease is not considered a form of gastritis

## Clinical picture

- Protein losing enteropathy is characteristic
  Excessive protein is lost from the thickened mucosa into the gut which results in hypoprotenemia and edema
- ***Gastric acid secretion is usually reduced or absent***
  This happens because mucosal cell hyperplasia replaces most of the parietal cells.
- Epigastric pain accompanied by nausea, vomiting anorexia and weight loss

| Overt bleeding is unusual but occult gastrointestinal bleeding may occur |
|---|

## Differential Diagnosis

DD includes conditions that may present with large gastric folds:
ZES
Malignancy
Infiltrative disorders eg sarcoidosis
Infectious etiology (CMV, Histoplasmosis, syphilis)

## Prognosis

These is an increased risk of adenocarcinoma of stomach in adults with menetrier's disease (CSDT)

# Carcinoma Stomach

## Risk Factors for Carcinoma Stomoch:

| Risk factors for stomach carcinoma : |
|---|
| 1. Long term ingestion of high concentration of nitrates in dried smoke and salted foods. Q |
| 2. Loss of gastric acidity - Atrophic gastritis Q<br>- Partial gastrectomy (peptic ulcer surgery) Q<br>- Pernicious anemia Q |
| 3. Infection with H. pylori Q |
| 4. Intestinal metaplasia Q *(metaplasia type II* and III) |
| 5. Gatric ulcer & polyps Q (Q *No association has been found between deodonal ulcer and gastric cancer*) |
| 6. Menetrier's disease Q: extreme hypertrophy of gastric rugal folds. |
| 7. Blood group A Q |
| 8. Cigarette smoking, Dust ingestion, Ingestion of spirits, Genetic factors have also been implicated. |

## Premalignant conditions for Gastric Adenocarcinoma:

| Premalignant lesions for Gastric Adenocarcinoma |
|---|
| • Chronic Atrophic Gastritis (H. pylori > Pernicious Anemia) |
| • Intestinal Metaplasia Type II and Type III<br>*(Intestinal Metaplasia type I is not associated with increased risk)* |
| • Gastric Dysplasia |
| • Gastric polyps (Adenomatous polyps)<br>*(Hyperplastic polyps are generally not considered premalignant as the rate of malignant transformation in these polyps is <1% and confined to polyps > 1cm)* |
| • Previous Gastrectomy |
| • Menetrier's Disease |
| • Gastric ulcers (long standing gastric ulcers : Low risk) |

***Gastric adenocarcinoma may be associated with long standing gastric peptic ulcers (small risk) but not with duodenal ulcers***

## Gastric Polyps and Premalignant Potential:

**Gastric Polyps and Premalignant Potential**

| Hyperplastic Polyps | Adenomatous Polyps |
|---|---|
| • Hyperplastic Polyps account for >75% of all gastric polyps | • Adenomatous Polyps account for < 25% of all gastric polyps |
| • These are not considered premalignant lesions and do not appear to have any significant malignant potential (< 1%) | • These are considered premalignant lesions They are most commonly found in the antrum of stomach and have significant malignant potential |

## The most common site of gastric adenocarcinoma:

- ***The most common site of gastric adenocarcinoma is antrum***
  *'40% tumors are in the antrum, predominantly on the lesser curvature, 30% arise in the body and fundus, 25% at the cardia and 5% involve the whole organ'- CSDT*
- **The most common site of Gastric Adenocarcinoma secondary to h.pylori Infection is Antrum**
- **The most common site of Gastric Adenocarcinoma secondary to Pernicious anemia is Fundus and Body**

| Gastric cancer secondary to: | Location / Site |
|---|---|
| H. Pylori | Antrum > body > fundus |
| Pernicoius Anemia | Fundus and body (not antrum) |

*Atrophic glands with extensive intestinal metaplasia are most charachteristically confined to the fundus in patients with pernicious anaemia.Gastric cancer in case of pernicious anemia is most often located in the fundus or body of the stomach rather in the Antrum.*

## Classification of Gastric Carcinoma

**Based on Layers of the stomach wall involved :**

| | |
|---|---|
| *Early gastric cancer:* | Cancer limited to the mucosa and submucosa with or without lymph node involvement. |
| *Late gastric cancer:* | Cancer involving the muscularis. |

**Based on Macroscopic Growth Pattern**

*In Ca Stomach, three macroscopic growth patterns are recognized, and may be evident in both early and advanced gastric cancer stages:*

a. Exophytic (Type I): Protruded in early stages, Cauliflower like polypoidal growth in advanced stages.

b. Flat or depressed (Type II) : With no obvious tumor mass in mucosa eg. Superficial spreading type

c. Excavated arc Ulcerated (Type III) : Shallow or deeply erosive crater is present in the wall of stomach.

- ***Early cases of type I & type II are potentially curable*** *- Bailey 22nd / 693*
  The prognosis depends on depth of invasion and extent of nodal and distant metastasis.
- ***Superficial spreading type indicates an early stage of type II malignancy. It therefore is potentially curable.***
- ***'Linitis plastica'*** is characterized by ***extensive infiltration of malignancy*** into a broad region of gastric wall or entire stomach creating a rigid, thickened *leather-bottle like stomach.*

**Guidelines for management of Gastric carcinoma:**

- Surgical resection remains the mainstay of treatment of gastric cancer either for cure or for palliation
- ***The extent of gastric resection*** depends on the site of tumor in the stomach.
  *Tumors in the distal third or antrum of stomach require a subtotal gastrectomy (partial gastrectomy) while tumors of the middle or proximal third of the stomach require a total gastrectomy*

| *Distal Third /Antrum Gastric cancer* | *Middle Third / Proximal Gastric cancer* |
|---|---|
| *Subtotal Gastrectomy* | *Total Gastrectomy* |

*Patients with curable cancers of the stomach should also undergo a D2 lymphadenectomy*

- ***The extent of resection of adjacent*** **structures (pancreas, spleen etc)** depends on the location of primary tumor and local invasion

  *Pancreatic Resection*

  The distal pancreas should not be removed a part of a resection for a cancer of the distal two third of the stomach (unless there is direct invasion)

  The distal pancreas should be removed only when there is direct invasion and still a chance of a curative procedure in patients with carcinoma of the proximal stomach

  *Splenic resection*

  *Splenectomy is not indicated unless the tumor directly invades the spleen or involves the splenic hilar lymph nodes.* Resection of spleen and splenic hilar lymph nodes *may be considered* in patients with *tumors of the proximal stomach* located in the greater curvature / posterior wall of the stomach close to the splenic hilum *where the incidence of splenic hilar nodal involvement is likely to be high*

*Splenic hilar lymph nodes are generally not involved in distal third / antral gastric cancers*

| Adjacent structure | Distal Third / Antrum Gastric cancer | Proximal Gastric cancer |
|---|---|---|
| *Pancreas* | • *Should not be removed routinely*<br>• *Resected if there is direct invasion* | • *Should not be removed routinely*<br>• *Resected if there is direct invasion and/or still a chance of curative procedure* |
| *Spleen* | • *Should not be removed routinely*<br>• *Resected if there is direct invasion or involvement of splenic hilar lymph nodes (This is unlikely)* | • *May require splenectomy to include the draining lymph nodes especially if lesion is located on the greater curvature / posterior wall, close to the splenic hilum* |

***The most common benign neoplasms of the stomach are Leiomyomas*** $^{Q}$.

# Malabsorption Syndrome and Disorders of Small Intestine

## Steatorrhea

***Steatorrhea*** *is typically defined as increased excretion of fat in stool (excretion of > 7.0 gm of fat in stool during 24 hours while the patient is on a diet containing no more than 100gm of fat per day).*
***Steatorrhea essentially represents malabsorption of fat.***

This may be caused by several conditions including:

- *Acute or chronic Liver disease / Biliary Disease*
- *Mucosal disease (eg. Celiac disease / Crohn's disease)*
- *Reduced absorptive surface (Small Bowel Syndrome)*
- *Reduced contact time (Laxative abuse, Carcinoid syndrome)*
- *Disturbed mesenteric blood supply (Mesenteric ischemia)*
- *Disturbed mesenteric lymphatic drainage (Tuberculosis, Malignancy)*
- ***Pancreatic exocrine deficiency (Reduced Pancreatic Lipase)***

## D-xylose test

*D-xylose is a carbohydrate that is absorbed almost exclusively in the proximal small bowel without the help of pancreatic enzymes. A positive D-xylose test indicates malabsorption due to intestinal mucosal disease and thus is used as a test for assessment of mucosal function.*

### D- Xylose Test

- D-Xylose *is a carbohydrate*[Q] that is absorbed completely in small bowel without the help of pancreatic enzymes and excreted unchanged in urine
- D- Xylose absorption test is used to distinguish *malabsorption*[Q] due to pancreatic disease from malabsorption due to intestinal mucosal disease
- D-Xylose is absorbed almost exclusively in the proximal small bowel (duodenum and jejunum), and a positive test primarily reflects a duodenal /Jejunal mucosal disease

*Malabsorption due to intestinal mucosal disease*

*Malabsorption due to pancreatic disease*

*25g of Dxylose is given orally and urine is collected at 5 hours*
*If D-xylose absorption is normal,*
*> 5gm of D- xylose appears in urine of 5 hours.*

- D-xylose is not absorbed normally as its absorption depends on mucosal surface area available
- Urine excretion of D-xylose < 5gm at 5 hours

*Positive D- xylose test*

- D- xylose is absorbed normally as its absorption does not require the help of pancreatic enzymes
- Urine excretion of D-xylose >5gm at 5 hours

Negative D- xylose test

*Pancreatic insufficiency is associated with a Negative D- xylose test (Normal D-xylose excretion)*

***D-xylose absorption test*** *is the most commonly employed test for carbohydrate absorption*

## Causes of Positive D-Xylose Test

D-xylose Test

| Positive test | False positive test |
|---|---|
| *Decreased (↓) D- Xylose excretion in urine due to malabsorption from gastrointestinal mucosal disease* | *Decreased D-xylose excretion in urine due to causes other than malabsorption from small bowel mucosal disease* |
| Causes Include | Causes Include |
| • ***Celiac disease*** <br>• *Tropical sprue* <br>• *Whipple's disease* <br>• *Other mucosal diseases* | • ***Bacterial overgrowth*** <br>• ***Renal insufficiency*** <br>• *Delayed gastric emptying* <br>• *Rapid intestinal transit* <br>• *Vomiting* <br>• ***Ascites /Pleural Effusion*** *(Third space collections)* |

- **Blind loop syndrome** may be associated with a reduced functional intestinal mucosa and bacterial overgrowth. This condition may thus lead to both, a positive or false positive D- xylose test depending on the pathophysiology involved.
  ***Blind loop syndrome*** and *Antibiotic therapy may cause false positive D-xylose test due to* ***bacterial overgrowth***
- **Pyloric stenosis** *may cause false positive results due to delayed gastric emptying and persistant vomiting.*
- **Ascitis** *is an established cause for false positive D- xylose test due to large collection of fluid in third space*

***After a positive D-xylose test is obtained, a jejunal biopsy should be performed to diagnose the mucosal abnormality***

## Evaluation of small intestine malabsorption of carbohydrates due to altered small intestinal mucosal function

| | |
|---|---|
| **Urinary D-xylose test** | Non invasive test of choice |
| **Endoscopic mucosal biopsy** | Test of choice / preferred test |

## Schilling Test:

- Schilling test is performed to determine the cause of cobalamine malabsorption.
- Since cobalamine absorption requires multiple steps including gastric, pancreatic and ileal processes, the Schilling test can also be used to assess the integrity of these other organs.
- The Schilling test is performed by administering Co58-labeled cobalamin orally and collecting urine for 24h
- The ***Schilling test may be abnormal (defined as less than 10 percent excretion in 24h) in conditions that affect cobalamine absorption including Pernicious anemia, Chronic Pancreatitis, Bacterial overgrowth syndrome and Ileal dysfunction***

| Conditions with Abnormal Schilling's Test (Abnormal Cobalamine Absorption) |
|---|
| ***Pernicious anemia*** <br>***Chronic Pancreatitis*** <br>***Achlorhydria*** <br>***Bacterial overgrowth syndrome*** <br>***Ileal dysfunction*** |

- The etiology for an abnormal Schilling test may be deduced by administering Co58-labeled cobalamin with intrinsic factor, pancreatic enzymes or after 5-day course of antibiotics. Differential Results of Schilling Test in various diseases associated with cobalamin malabsorption may thus help establish the diagnosis.

| Diagnosis | $^{58}$Co-Cbl | With Intrinsic Factor | With Pancreatic Enzymes | After 5 Days of Antibiotics |
|---|---|---|---|---|
| Pernicious anemia | *Reduced* | *Normal* | *Reduced* | *Reduced* |
| Chronic pancreatitis | *Reduced* | *Reduced* | *Normal* | *Reduced* |
| Bacterial overgrowth | *Reduced* | *Reduced* | *Reduced* | *Normal* |
| Ileal disease | *Reduced* | *Reduced* | *Reduced* | *Reduced* |

## Differential Diagnosis of Various conditions presenting with Malabsorption using D-Xylose, Schilling's Test and Mucosal Biopsy

| | D-Xylose Test | Schilling Test | Duodenal Mucosal Biopsy |
|---|---|---|---|
| Chronic pancreatitis | Normal | 50% abnormal; if abnormal, normal with pancreatic enzymes | Normal |
| Bacterial overgrowth syndrome | Normal or only modestly abnormal | Often abnormal; if abnormal, normal after antibiotics | Usually normal |
| Ileal disease | Normal | Abnormal | Normal |
| Celiac sprue | Decreased | Normal | Abnormal: probably "flat" |
| Intestinal lymphangiectasia | Normal | Normal | Abnormal: "dilated lymphatics" |

## Malabsorption syndromes based on lesions seen on intestinal Biopsy

**Lesions seen on a small bowel biopsy**

**Specific**

**Diffuse Specific**
*Whipples Disease*
*Agammaglobulinemia*
*Abetalipoproteinemia*

**Patchy Specific**
*Intestinal lymphoma*
*Intestinal lymphangiectasia*
*Eosinophilic gastroenteritis*
*Amyloids*
*Amyloidosis*
*Crohn's disease*
*Infection by one or more microorganisms*
*Mastocytosis*

**Non Specific**
(Biopsy is not diagnostic)

**Diffuse Non Specific**
*Celiac sprue*
*Tropical sprue*
*Bacterial overgrowth*
*Folate deficiency*
*Vitamin B12 deficiency*
*Radiation enteritis*
*Zollinger-Ellison syndrome*
*Protein-calorie malnutrition*
*Drug-induced enteritis*

## Disease that can be Diagnosed by Small-Intestinal Mucosal Biopsies

| Lesions | Pathologic Findings |
|---|---|
| Diffuse, specific | |
| • *Whipple's disease* | Lamina propria contains macrophages containing PAS + material |
| • *Agammaglobulinemia* | No plasma cells; either normal or absent villi ("flat mucosa") |
| • Abetalipoproteinemia | Normal villi; epithelial cells vacuolated with fat postprandially |
| Patchy, specific | |
| • *Intestinal lymphoma* | Malignant cells in lamina propria and submucosa |
| • *Intestinal lymphangiectasia* | Dilated lymphatics; clubbed villi |
| • *Eosinophilic gastroenteritis* | Eosinophil infiltration of lamina propria and mucosa |
| • *Amyloidosis* | Amyloid deposits |
| • *Crohn's disease* | Noncaseating granulomas |
| • *Infection by one or more microorganisms* | Specific organisms |
| • *Mastocytosis* | Mast cell infiltration of lamina propria |
| Diffuse, nonspecific | |
| • *Celiac sprue* | Short or absent villi; mononuclear infiltrate; epithelial cell damage; hypertrophy of crypts |
| • *Tropical sprue* | Similar to celiac sprue |
| • *Bacterial overgrowth* | Patchy damage to villi; lymphocyte |
| • *Folate deficiency* | Short villi; decreased mitosis in crypts; megalocytosis |
| • *Vitamin B12 deficiency* | Similar to folate deficiency |
| • *Radiation enteritis* | Similar to folate deficiency |
| • *Zollinger – Ellison syndrome* | Mucosal ulceration and erosion from acid |
| • *Protein –calorie malnutrition* | Villous atrophy; secondary bacterial overgrowth |
| • *Drug-induced enteritis* | Variable histology |

# Celiac Disease

**Celiac disease**

Malabsorption syndrome of non-infectious etiology without systemic features.

**Etiology**

| Environmental factors | Immunogenic factors | Genetic factors |
|---|---|---|
| Intolerance to ***gliadin*** a component of gluten, present in wheat, barley, rye and oats | Ig A antibodies are present<br>- ***IgA antiendomysial***<br>- IgA antigliadin<br>- IgA anti tissue tranglutaminase<br>***Antiendomysial antibody has 90-95% Sensitivity and 90-95% Specificity*** | 95% express<br>***HLA-OQ2 allele***[Q] |

**Presentation**

Malabsorption of multiple nutrients with diarrhea, steatorrhea, weight / loss and consequences of nutrients depletion i.e. anemia and metabolic bone disease

or

Malabsorption of a single nutrient, with iron deficiency anemia or folate deficiency or osteomalacia or edema from protein loss.

**Diagnosis**

1. **Small intestinal biopsy (duodenal/jejunal)**[Q]
   (Charachteristic but not diagnostic)[Q]
   Absence or reduced height of villi
   (Flat appearnce)[Q]
   - Crypt hyperplasia, villous atrophy
     (But not mucosal atrophy)[Q]
   - Cuboidal appearance of epethelial cells and increased intraepethelial lymphocytes
   - Increased lymphocytes and plasma cells in lamina propria[Q]

**2. Antiendomysial antibodies**[Q]
Antiendomysial antibody has 90-95% sensitivity and 90-95% specificity.
*Prompt clinical and histopathological response, together with disappearance of Ig Antiendomysial antibodies following institution of a gluten free diet is diagnostic.*

| Associated disease[Q] | Complications |
|---|---|
| • Dermatitis Herpetoformis[Q]<br>• Diabetes mellitus type I[Q]<br>• IgA deficiency | • Increased incidence of both gastro intestinal and non gastrointestinal neoplasms as well as ***Intestinal lymphomas.***[Q] |

**Management**

Gluten free diet + Glucocorticoids or immunosupressive agents.[Q]

## Approach to diagnosis of Celiac Disease

**Typical symptoms of Celiac disease**

*Chronic Diarrhea*[Q]
*Weight's loss*[Q]
*Abdominal distension*[Q]
*Growth Retardation*[Q]

**Findings or routine laboratory tests**

- Anemia *(Microcytic or Megaloblastic)*
- ***Mild elevation of aminotransferases in upto 40% of patients***
- *↑PT / ↓Vit A or Vit D*
  *(Reflect impaired absorption of fat soluble vitamins*
- *Low serum $Ca^{++}$ / ↑Alk. Phos*
  *(Reflct impaired $Ca^{++}$ or vit D absorption.*

Suspect diagnosis of celiac disease and confirm/exclude by performing relevant serological tests

| Serological tests | | |
|---|---|---|
| Two tests with highest diagnostic accuracy are | | |
| *IgA Endomysial Antibody* | : | *≥ 90% sensitivity* |
| *IgA ↓TGA Antibody* | : | *≥ 95% Specificity* |

***Antigliaden antibodies are no longer recommended because of their low sensitivity and specificity.***

## Diagnosis of Celiac Sprue

| Serological tests ⟶ | Endoscopic mucosal biopsy *of distal duodenum or proxi- mal jejunum* ⟶ | Prompt clinical and histo-pathological response follo-wing institution of gluten free diet. |
|---|---|---|

| Serological tests (*CMDT*) | Endoscopic mucosal biopsy | Diagnosis |
|---|---|---|
| ▪ ***Two serological tests with highest diagnostic accuracy are***<br>1. IgA antiendomysial antibody<br>2. IgA anti – tTG antibody<br>▪ Both tests have a > 90% sensitivity and > 95% specificity. | • Findings are ***characteristic but not specific / diagnostic.***<br>• Biopsy of distal duodenum or proximal jejunum is performed.<br>• Finding are restricted to mucosa and include :<br>– Loss or blunting of villi / flat villi<br>– Hypertrophy of intestinal crypts<br>– Infiltration of lamina propria will lymphocytes / plasma cells<br>– Cuboidal appearance of epithelial cells and increased intraepithelial lymphocytes. | • **Diagnosis of celiac sprue requires** Presence of characteristic histopathological changes on biopsy together will prompt clinical and hispathological response following institution of gluten free diet.<br>• IgA antiendomysial Ab or IgA anti – tTGA Ab should also disappear after a gluten free diet. |
| IgG or IgA antigliadin antibodies are present in 85% of patients with celiac sprue. However their specificity is relatively low (80 – 90%) which limits their usefulness as screening test. | | |
| *Small bowel biopsy is still recommended to confirm diagnosis.* | | |

**Antiendomysial antibody > Anti tissue transglutaminase antibody > Antireticular antibody> Antigliadin antibody**

| **Antigliadin (IJP) Antibodies (AGN)** | **Anti reticulin IJP Antibodies (ARA)** | **Antiendomysial Antibiotics (Anti EMA)** | **Anti tissue transglutaminase antibody (Anti-tTGA)** |
|---|---|---|---|
| • First immunological assay to be tested were antigliadin antibodies.<br>• The variability and lower accuracy make them *unsuitable for diagnostic and screening purposes*<br>• Antigliadin assays have been replaced by more specific and sensitive tests using other antibodies | • Second antibody identified in literature was the antireticulin antibodies.<br>• There are atleast 5 types of antireticulin antibodies but only one type is associated with celiac disease.<br>• These antibodies are *not very sensitive and are not used in routine practice.* | • Antiendomysial antibodies have ***high sensitivity and specificity*** for the diagnosis of celiac disease.<br>• These antibodies are directed against endomysium or 'Intermyofibril substance' of smooth muscle.<br>• The antigen recognized by these antibodies is 'tissue transglutaminase'. | • Major breakthrough for serological diagnosis of celiac disease.<br>• Antitissue transglutaminase antibodies (Anti-tTGA ) are ***also highly sensitive and specific but performance of anti EMA is superior to Anti-tTGA*** |

***Pathologic morphology of celiac disease:***

The mucosa appears flat or scalloped or may be visually normal. Biopsy specimens demonstrate diffuse enteritis, with the following features.

| Small Intestinal Biopsy (duodenal /jejunal) in Celiac disease (Characteristic but not diagnostic$^{Q}$) |
|---|
| • *Absence or reduced height of villi (Flat appearance)$^{Q}$*<br>• *Crypt hyperplasia, villous atrophy (but not mucosal atrophy)$^{Q}$*<br>• *Cuboidal appearance of epithelial cells and increased intraepithelial lymphocytes*<br>• *Increased lymphocytes and plasma cells in lamina propria$^{Q}$* |

| The villi | The surface epithelium | The crypts | The lamina propria |
|---|---|---|---|
| show marked atrophy or total loss. | shows vacuolar degeneration, loss of the microvillus brush border, and an increased number of intraepithelial lymphocytes. | exhibit increased mitotic activity and are elongated, hyperplastic and tortuous, so the overall mucosal thickness remains the same. | has an overall increase in plasma cells, lymphocytes, macrophages, eosinophils and mast cells. |

*All these **structural changes are more marked in the proximal small intestine** Q than in the distal because it is the duodenum and proximal jejunum that are exposed to the highest concentration of the dietary gluten.*

***The overall mucosal thickness remains the same in Celiac Disease***
***Mucosal atrophy and presence of Giardia Lambia are not seen in biopsy from celiac disease.***



## Associations of Celiac Disease:

Associations of Celiac Disease (CMDT & Harrisons)

- ***Dermatitis Herpetiformis***
- Other autoimmune disease including: *(CMDT)*
  - *Addison's disease*
  - *Grave's disease*
  - *Diabetes mellitus- Type I (Harrisons)*
  - *Myaesthenia Gravis*
  - *Slogren syndrome*
  - *Atrophic Gastritis*
  - *Pancreatic insufficiency*
- IgA deficiency *(Harrisons)*
- Lymphomas *(Harrisons)*

**Note**

**Celiac disease is associated with an increased risk of cancer including Lymphomas (NHL, Intestinal T cell Lymphoma)**

*The possibility of Lymphoma must be considered whenever a patient with celiac sprue previously doing well on a gluten free diet is no longer responsive to gluten free diet' - Harrisons*

## Vitamin Deficiency in Patients with Celiac disease:

**Vitamin Deficiency in Patients with Celiac disease**

| Fat Soluble Vitamins | Other Vitamins |
|---|---|
| *Vitamin A (common)* | • *Folic acid (common)* |
| *Vitamin D (common)* | • *Vitamin $B_{12}$ (uncommon)* |
| *Vitamin E (uncommon)* | |
| *Vitamin K (uncommon)* | |

## Treatment of Celiac Disease:

*The mainstay of treatment for celiac sprue is administration of of a glutin free diet.*
*'Removal of all glutin from the diet is essential to therapy'. -- CMDT*

# Whipple's Disease

**Whipple's Disease**

*Malabsorption syndrome with systemic features with infectious etiology*

**Etiology**

*Gram negative actinomycete*[Q] *Tropheryma whippelii*

**Biopsy/ Histopathology**

*Biopsy is Abnormal and specific/diagnostic*

***The Hallmark of Whipple's disease is a** small intestinal mucosa laden with macrophages. **Accompanying changes include** lymphatic dilatation **suggesting lymphatic blockage. The lymphatic blockage is believed to be responsible for** lipid deposition **in the villi** – Robbins*

**Histopathological findings in Whipple's disease**

| Characterisitc findings / Specific finding (Hallmark of disease) | Associated findings |
|---|---|
| • Small intestinal mucosa laden with ***foamy macrophages in the lamina propria***, which are characteristically, Periodic – Acid – Schiff (PAS) positive.<br>• These PAS positive macrophages (monocytes) also *contain gram positive – acid fast bacillus T. whipleii*[Q]. (The substance in macrophages that stains positive with PAS is thought to be remnants of the cell wall of phagocytosed bacilli)<br>Note :<br>*PAS positive macrophages are not pathognomic for Whipple's disease. They have also been isolated in other diseases eg. Mycobacterium Avium Intercellulare & Mycobacterium Tuberculosis.* | • Villi may be thickenned, widened or blunted<br>• Small intestinal mucosal and ***submucosal lymphatic vessels are dilated***<br>• Lipid droplets / Lipid vacuoles / ***Lipid deposition may be seen***<br>• The number of lamina propria plasma cells, ***lymphocytes*** and eosinophills ***are decreased***<br>*(Samter's Immunologic Diseases by Austen and Samter 2nd /704)*<br>*'The number of intraepethelial lymphocytes is not increased'*<br>*(Sternberg's Diagnostic Surgical Pathology 4th/1481)* |

**Presentation**

*Features of malabsorption*

Multisystemic involvement along with Fever, Lymphadenopathy and Arthralgias [Q]

- *CNS invovement is seen in about 10%* of patients. Manifestations include
  - ***Dementia*** [Q] (confusion and memory loss)
  - Seizures, Coma, Myoclonus [Q]
- *Cranial N. findings* include Nystagmus and Ophthalmoplegia [Q]

Non specific symptoms like Confusion and Memory loss (Dementia) in all likelihood, should be more common a presentation than seizures.

***Ophthalmopegia is due to cranial nerve involvement and not supra-nuclear in type.***

***Treatment***

Etiology is infectious so treatment is with Antibiotics

**Trimethoprim+sufamethoxocate**

## Differential Diagnosis of the three major forms of Malabsorption Syndromes:

| *Whipple's Disease* | *Tropical Sprue* | *Coeliac Disease* |
|---|---|---|
| Malabsorption syndrome with systemic features with infectious etiology | Malabsorption syndrome of infectious etiology without systemic features | Malabsorption syndrome of non infectious etiology without systemic features |
| **Etiology** | **Etiology** | **Etiology** |
| Gram negative actinomycete[Q] Tropheryma whippelii | Caused by some strains of E.coli | Caused by intolerance to 'gliadin' gluten a protein found in wheat rye, barley[Q]. |
| **Biopsy** | **Biopsy** | **Biopsy** |
| **Biopsy is Abnormal and specific/diagnostic** | **Biopsy is abnormal but not specific/diagnostic** | **Biopsy is abnormal but not specific/diagnostic** |
| Lamina Propria is infiltrated with macrophages containing PAS positive glycoproteins and rod shaped bacilli<br>Dilated lymphatics | Shortened, thickened villi increased crypt depth infiltration by mononuclear cells | Blunting and flattening surface with villi either absent or broad and short<br>Crypts are elongated<br>Dense infiltration of inflammatory cells in lamina propria |
| **Clinical features** | **Clinical features** | **Clinical features** |
| Features of malabsorption<br>+ Array of systemic features | Features of malabsorption | Features of malabsorption |
| **Management** | **Management** | **Management** |
| Etiology is infectious so treatment is with Antibiotics<br>Trimethoprim+sufamethoxocate | Etiology is infectious so treatment is with antibiotics (Sulfonamide/ Tetracycline) | Etiology is not infectious but immune<br>Glutin free diet (no antibiotics) +<br>Glucocorticoids or immunosuppressive agents |

## Intestinal Angina

**What is Intestinal Angina : Journal of Emergency Medicine : Review Article.**

- Intestinal angina refers to the clinical syndrome seen in association with ***Chronic Mesenteric Ischaemia.***
- It is characterized by reduced mesenteric blood flow that interferes with physiological function but does not cause infarction.
- Mesentric angina is the result of intestinal hypoperfusion through two of the three major vessels supplying the small intestine.
  - Superior Mesentric Artery
  - Celiac artery
  - Inferior Mesentric Artery

**Presentation**

- Post Prandial Abdominal Pain: *Abdominal pain that starts about 30 minutes after eating and lasts for one to two hours.*
- Fear of eating and weight loss: Once the patient realizes the relationship between eating and pain.
- Diarrhea, Nausea, Vomiting

**Diagnosis**

*Gold standard for confirmation of mesenteric arterial occlusion (**chronic** mesenteric ischaemia) is Angiography*
*(Note that Gold standard for diagnosis of **acute** mesenteric ischaemia is Laparotomy[Q]. Surgical exploration should not be delayed).*

## Short Bowel Syndrome

**Short bowel syndrome:** *(Myriad of clinical problems that follow resection of warying length of small intestine)*

**Causes:**

1. *Mesentric vascular disease: mesenteric ischaemia*[Q]
2. *Primary mucosal and submucosal disease – Crohn's disease*[Q]
3. *Operations without preexisting small intestinal disease – jejunoilial bypass for obesity*[Q]

**Manifestation resulting from resection of varying length of small intestine**

| Diarrhea and Steatorrhea [Q] | ↑ed Renal calcium oxalate calculi | ↑ed Cholesterol gall stones [Q] | Gastric hypersecretion of acid [Q] |
|---|---|---|---|
| Multiple factors contribute to diarrhea and steatorrhea such as:<br>• Absence of intestinal mucosa required for absorption of lipid and fluid and electrolytes<br>• Stimulation of colonic fluid and electrolyte secretion by increased bile acids that enter colon<br>• Decreased intestinal transit and bacterial overgrowth from absence of ilio caecal valve<br>• Reduced pH in duodenum from gastric acid hypersecretion. | • There occurs increased absorption of oxalates by large intestine in patients with a small intestinal resection with intact colon<br>• Hyperoxaluria and renal calcium oxalate crystals form<br>**Treatment:**<br>• Dietry restriction of oxalate containing feed (spinach, tea)<br>• Cholestyramine an anion binding resin and calcium | Due to a decrease in the bile acid pool size and resulting super saturation of cholesteral in gall-bladder bile. | Related to reduced hormonal inhibition of acid secretion or increased gastrin levels due to reduced small intestine catabolism of gastrin. |

***Short bowel syndrome is characterized by increased gastrin levels (hypergastrinemia) due to reduced small intestinal catabolism of gastrin***

**Vitamin Deficiencies in Short Bowel Syndrome:**

*Vitamin Deficiencies in Short Bowel Syndrome*

**Short Bowel Syndrome with Extensive Jejunal Resection**

- This is associated primarily with deficiency of fat soluble vitamins (A, D, E, K)
- *The most common fat-soluble vitamins that are deficienct are vitamin A and D and to a lesser extent vitamin E followed by vitamin K.*

Vitamin A, D > Vitamin E >> Vitamin K

**Deficiency of vitamin K is uncommon as vitamin K is synthesized by colonic bacteria**

- 60% of vitamin K is synthesized by colonic bacteria
- 40% of vitamin K is received by dietary intake
- *Deficiency of vitamin K is therefore uncommon in patients with short bowel syndrome who have an intact colon.*
- *Deficiency of vitamin K is however common in those patients with short bowel syndrome who do not have a residual colon.*

**Short Bowel Syndrome with Extensive ileal resection**

- This is associated primarily with deficiency of vitamin B12 since vitamin B12 is only absorbed in the terminal ileum.
- Fat soluble vitamin deficiencies may also occur due to fat malabsorption from decrease in concentration of bile acids / salts.

(Bile acids are absorbed only from the ileum)

Vitamin B12 > Fat solubleVitamin

*The ileum has the capacity to adapt and compensate for jejunal resection. The jejunum does not have the capacity to adapt and compensate for ileal resection (as the terminal ileum has the exclusive capacity to reabsorb bile salts &vit $B_{12}$)*

***Cyanocobalamine (Vitamin B12) deficiency is the most common deficiency in patients with short bowel syndrome associated with loss of ileum (ileal resection) since vitamin B12 is absorbed only in the ileum.***

## Inflammatory Bowel Disease

# Ulcerative Colitis and Crohn's Disease

**DISTINGUISHING FEATURES OF CROHN'S DISEASE AND ULCERATIVE COLITIS :**

| FEATURE | CROHN'S DISEASE | ULCERATIVE COLITIS |
|---|---|---|
| **A. Macroscopic features** | | |
| *1. Distribution* | Segmental with ***skip areas*** Q | Continuous *without skip areas* Q |
| *2. Location* | Commonly terminal ileum and /or ascending colon | Commonly rectum sigmoid colon and extending upwards |
| *3. Extent* | Usually involves the entire thickness of the affected segment of bowel wall | Usually superficial, confined to mucosal layers |
| *4. Ulcers* | Serpiginous ulcers, that may develop into deep *Fissures* Q | Superficial mucosal ulcers without fissures |
| *5. Pseudopolyps* | Rarely seen | *Commonly present* Q |
| *6. Fibrosis* | Common | Rare |
| *7. Shortening* | Due to fibrosis | Due to contraction of muscularis |
| **B. Microscopic features** | | |
| *1. Depth of inflammation* | *Typically transmural* Q | *Mucosal* Q and Submucosal |
| *2. Type of inflammation* | *Non-caseating granulomas* Q and infiltrate of mononuclear cells (lymphocytes, plasma cells and macrophages) (Crypt abscess may also be seen) | *Crypt abscess* and non-specific acute and chronic inflammatory cells (lymphocytes, plasma cells neutrophils, eosinophils, mast cells) |
| *3. Mucosa* | Patchy ulceration | Hemorrhagic mucosa with ulceration |
| *4. Submucosa* | Widened due to edema and lymphoid aggregates | Normal or reduced in width |
| *5. Muscularis* | Infiltrated by inflammatory cells | Usually spared, except in cases of ***Toxic Megacolon*** Q |
| *6. Fibrosis* | Present | Usually absent |
| **C. Complications** | | |
| *1. Fistula formation* | Internal and external fistulae in 10% cases | *Extremely rare* Q |
| *2. Malignant changes* | Less common but present | May occur in disease of more than 10 years duration (*more common* Q) |
| *3. Fibrous strictures* | *Common* Q | *Never* Q |
| *4. Toxic Megacolon* | -- | Risk present Q |
| 5. Named Features | *Hose pipe appearance* Q *Cobble-Stone appearance* Q | *Garden hose appearance* Q *Pseudopolyps* Q |

**Serological Markers for Inflammatory Bowel Disease**

Serological markers for inflammatory bowel disease

| Perinuclear Antineutrophil Cytoplasmic Antibodies (p ANCA) | Antisaccharomyces Cerevisiae Antibodies (ASCA) |
|---|---|
| • Positive in 60 - 70% of U.C. patients (and 5 - 10% of CD patients) | • Positive in 60 - 70% of CD patients (and 10 - 15% of U.C. patients) |

- *p ANCA +ve with ASCA -ve = 97% specificity for UC*
- *p ANCA +ve with ASCA +ve = 97% specificity for CD*

| Antibody | G.I. Disorder |
|---|---|
| *Antiendomysial antibody* Q | *Celiac sprue* |
| *Antisaccharomyces cerevisiae antibody* Q | *Crohn's disease* |
| *Antineutrophilic cytoplasmic antibody* Q | *Ulcerative colitis* |

## Extraintestinal diseases associated with inflammatory bowel disease:

| Joint manifestations: | Ocular manifestations: | Skin manifestations: | Hepatic manifestations: |
|---|---|---|---|
| Arthralgia to acute arthritis | Episcleritis | Erythema nodosum | Nonspecific focal hepatitis |
| Ankylosing spondylitis | Recurrent iritis | Pyoderma gangrenosum$^{Q}$ | Fatty liver |
| Sacroilitis | Uveitis | **Aphthous ulcers** | Pericholangitis |
| | | | **Sclerosing cholangitis** |
| | | | Autoimmune chronic active hepatitis |
| | | | **Cirrhosis** |

| | Ulcerative Colitis | Crohn's Disease |
|---|---|---|
| **Clinical** | | |
| ***Gross blood in stool*** | ***Yes*** | ***Occasionally*** |
| ***Mucus*** | ***Yes*** | ***Occasionally*** |
| Systemic symptoms | Occasionally | Frequently |
| Pain | Occasionally | Frequently |
| Abdominal mass | Rarely | Yes |
| Significant perineal disease | No | Frequently |
| Fistulas | No | Yes |
| Small-intestinal obstruction | No | Frequently |
| Colonic obstruction | Rarely | Frequently |
| Response to antibiotics | No | Yes |
| Recurrence after surgery | No | Yes |
| ***ANCA-positive*** | ***Frequently*** | ***Rarely*** |
| ASCA –positive | Rarely | Frequently |
| **Endoscopic** | | |
| Rectal sparing | Rarely | Frequently |
| Continuous disease | Yes | Occasionally |
| Cobblestoning | No | Yes |
| Granuloma on biopsy | No | Occasionally |
| **Radiographic** | | |
| Small bowel significantly abnormal | No | Yes |
| Abnormal terminal ileum | Occasionally | Yes |
| Segmental colitis | No | Yes |
| Asymmetric colitis | No | Yes |
| Stricture | Occasionally | Frequently |
| **Epidemiology of IBD** | | |
| Age of onset | 15-30 and 60-80 | 15-30 & 60-80 |
| Male : Female ratio | 1:1 | ≈1.5 : 1 |
| Smoking | May prevent disease | May cause disease |
| Oral contraceptives | No increased risk | Odds ratio 1.4 |
| Appendectomy | Protective | Not protective |
| Monozygotic twins | 6% concordance | 58% concordance |
| Dizygotic twins | 0% concordance | 4% concordance |

## Management Protocol for Inflammatory Bowel Disease:

*The mainstay of therapy for inflammatory bowel disease remains 5- Aminosalicylic derivatives*

## Colonic Disorders

# Irritable Bowel Syndrome (IBS)

## Charachterisitc Symptoms and Diagnostic Criteria for Irritiable Bowel Syndrome (IBS)

**Symptoms that cumulatively support the diagnosis of Irritable Bowel Syndrome:**

- *Abnormal stool frequency[Q] (for research purposes, "abnormal" defined as > 3 bowel movements/week)*
- *Abnormal stool formation[Q] (lumpy/hard or loose/watery stool)*
- *Abnormal stool habits[Q] (straining, urgency, or feeling of incomplete evacuation)*
- *Passage of mucus[Q]*
- *Bloating or feeling of abdominal distention*

*The diagnosis of a functional bowel disorder always presumes the absence of a structural or biochemical explanation for the symptoms.*

**Diagnostic criteria for Irritable Bowel Syndrome**

Recurrent abdominal pain or discomfort at least 3 days per month in the last 3 months associated with two or more of the following

1. *Improvement with defecation[Q]*
2. *Onset associated with a change in frequency of stool[Q]*
3. *Onset associated with a change in form (appearance) of stool[Q].*

*Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis.*
*Discomfort means an uncomfortable sensation not described as pain. In pathophysiology research and clinical trails, a pain/discomfort frequency of at least 2 days a week during screening evaluation is required for subject eligibility.*

## Red flag" conditions in irritable bowel syndrome that suggest possibility of another disease

**"Red flag" conditions in irritable bowel syndrome that suggest possibility of another disease**

Presence of any of the following calls for further investigation to rule out other disease processes:

- *Fever*
- *Blood in stools*
- *Nocturnal pain*
- *Abnormal physical findings*
- *Onset in patients>50 years of age*
- *Weight loss or anorexia*
- *Anemia*
- *Abnormal blood studies*
- *Family history of inflammatory bowel disease or malignancy*

### IBS may be associated with diarrhea or constipation

*The most common pattern in IBS is constipation alternating with diarrhea*

### Young age and Female sex are epidemiological risk factors for IBS

*Onset in patients>50 years of age is a red flag sign and raises the possibility of another condition*

### IBS may be associated with Anxiety and stress

*Onset of symptoms in periods of stress supports a diagnosis of IBS.*

### IBS is charachteristically associated with absence of blood in stool

*Presence of blood in stool is a 'Red Flag' sign that suggests possibility of another disease.- Harrison's 17th/1901*

### Irritable Bowel syndrome (IBS) is a benign functional bowel disorder

*IBS does not predispose to malignancy in the long term*

## Possible Drugs for a Dominant Symptom in IBS: *(Harrison's 18th/2501)*

| Diarrhea | Constipation | Abdominal Pain |
|---|---|---|
| • *Lopepramide*<br>• *Cholestyramine resin*<br>• *Alosetron* | • *Psyllium husk*<br>• *Methylcellulose*<br>• *Calcium polycarbophil*<br>• *Lactulose syrup*<br>• *70% sorbitol*<br>• *Polyethylene glycol 3350*<br>• *Lubiprostone (Amitiza)*<br>• *Magnesium hydroxide* | • *Smooth-muscle relaxant*<br>• *Tricyclic antidepressants*<br>• *Selective serotonin reuptake inhibitors* |

# Colorectal Carcinomas

## Hereditary gastrointestinal polyposis syndromes

| Non-malignant polyps[Q] (Rare/Small Malignant potential) | |
|---|---|
| *Hamartomatous polyps*[Q] | *Hyperplastic polyps*[Q] |
| *Juvenile* ***polyposis***[Q]<br>*Peutz Jeghers syndrome*[Q] | |

| Malignant polyps[Q] |
|---|
| *Adenomatous Polyps*[Q] |
| ***Familial adenomatous polyposis***[Q]<br>*Gardner's syndrome*[Q]<br>*Turcot's syndrome*[Q]<br>*Lynch syndrome*[Q] |

## Review of Hereditary gastrointestinal polyposis syndromes

**Hereditary *autosomal dominant*[Q] gastrointestinal polyposis syndromes**

↓

| High Malignant Potential[Q] *(Histologically adenomas[Q])* | | |
|---|---|---|
| Syndrome | **Distribution** | **Associated** |
| **Familial colonic Polyposis** | Large intestine | None |
| **Gardner's syndrome** | *Large intestine > small intestine* | Osteomas<br>Lipomas<br>Fibromas<br>Epidermal cyst<br>*Ampullary Ca*<br>Desmoid |
| **Turcot's syndrome** | Large intestine | Brain Tumours |

↓

| Rare (small) Malignant Potential[Q] *(Histologically hamartomas[Q])* | | |
|---|---|---|
| **Syndrome** | **Distribution** | **Associated** |
| **Peutz Jagher's syndrome** | SI > LI > Stomach | **Mucocutaneous pigmentations**<br>Tumours of ovary, Breast, pacnreas, endometrium |
| **Juvenile polyposis syndrome** | LI > SI > Stomach | Various congenital abnormalities |

## Clues to Diagnosis for Heriditable (Autosomal dominant) Gastrointestinal polyposis syndromes:

***Neoplastic polyps***:

***Multiple Adenomalous polyps (Adenomas)*** - are a very common risk factor for colorectal malignancy. Infact if the polyposis is not treated surgically, colorectal cancer will develop in almost all patients (100%), before age 40

**Clues to diagnosis:**

| | |
|---|---|
| Adenomas in large intestine with no associated lesions | **Familial Polyposis coli** |
| Adenomas in large intestine associated with osteomas, fibromas or lipomas | **Gardner's Syndrome** |
| Adenomas in large intestine associated with brain tumors | **Turcot's syndrome** |

***Non-Neoplastic Polyps***: Peutz Jegher's syndrome and Juvenile polyposis, are two autosomal dominant, heritable conditions, associated with polyps in G.I.T. These polyps are however harmatomas and do not have malignant potential.

**Clues to their diagnosis:**

| | |
|---|---|
| Hamartomatous polyps throughout GIT associated with mucocutaneous pigmentation and tumors of pancreas ovary, breast, lung, uterus. | **Peutz Jeghers Syndrome** *(in small intestine[Q] > Large intestine[Q] > Stomach[Q])* |
| Hamartomatous polyps throughout GIT associated with various congenital anomalies. | **Juvenile Polyposis** *(in large Intestine[Q] > small intestine[Q] > stomach[Q])* |

## Peutz-Jegher's syndrome

***Mucocutaneous pigmentation along with gastrointestinal manifestations of abdominal pain and anemia suggest the diagnosis of Peutz-Jegher's syndrome.***

### Peutz Jagher's Syndrome

Peutz-Jaghers syndrome is a rare autosomal dominant, inherited syndrome characterized by mucocutaneous pigmentation and gastrointestinal polyposis.

*Autosomal Dominant Inheritance*[Q]
*Family history often positive*[Q]

| Mucocutaneous Pigmentation | Gastrointestinal Polyposis | Neoplasm's of Non intestinal organs |
|---|---|---|
| • Mucocutancous pigmentation involving lips, buccal mucosa and skin is characteristic (Digits, nails, pains, soles genitalia or any mucosal surface may be involved) | • Hamartomatous polys (Harrison's) Small intestine > Large intestine > Stomach<br>May present with:<br>Intussusception or obstruction<br>(Abdominal pain, bleeding, Anemia)<br>*Although hamartomas are not malignant, a small percentage of patients (13%) may develop malignancies of intestinal organs specially stomach and duodenum* | • Patients with this syndrome have increased risk of developing carcinomas of<br>- Ovary<br>- Breast<br>- Pancreas<br>- Endometrium |

| *Syndrome*[Q] | *Distribution*[Q] | *Histological type*[Q] | *Malignant potential*[Q] | *Associated*[Q] |
|---|---|---|---|---|
| Peutz Jegher's Syndrome | Small intestine > Large intestine > stomach | Hamartoma | Rare | • Mucocutaneous pigmentation<br>• Tumors of non-intestinal organs<br>- Ovary,<br>- Breast<br>- Pancreas<br>- Endometrium |

*Although hamartomas are not malignant, a small percentage (13%) of patients develop malignancies*[Q] *of intestinal organs, specially stomach and duodenum (NOT COLON).*

## Prognostic Factors for Colorectal Carcinoma:

***The most important prognostic factor of colorectal carcinoma is the 'stage of disease'.***

*The 'stage of disease' gives information related to depth of penetration into bowel wall and extent of regional lymph node spread, both of which are the two most important independent prognostic factors.*

| Most important prognostic factors |
|---|
| *'Extent of Regional Lymph node spread' and 'Depth of tumor invasion' are the most important determinants of prognosis* |

| **Single most important prognostic factor** | **Single most important <u>independent</u> prognostic factor** |
|---|---|
| *Stage of disease*[Q] | *Lymph node status*[Q] |

*Stage of disease gives information on both the depth of tumor penetration into the bowel wall and the extent of regional lymph node involvement*

***'Stage' of disease is a superior prognostic factor in comparison to Lymph node status alone***

*Single most important <u>independent</u> prognostic factor is the Lymph nodal status or the number of positive nodes*

*- Devita 7th / 1069*

*- Gastrointestinal Oncology (2004) / 684*

## Pancreatic Disorders

### Pancreatitis

**Ranson's criteria for prognosis in acute pancreatitis include:** (Adverse factors)

| At the time of Admission | During initial 48 hours |
|---|---|
| 1. *Age > 55 years* Q | 1. *Fall in haematocril > 10%* |
| 2. *Leucocytosis > 16.000/µl* Q | 2. *Fluid deficit > 4000 ml* |
| 3. *Hyperglycemia > 200 mg/dl* | 3. *Hypocalcemia < 8 mg/dl* Q |
| 4. *Serum LDH > 400 IU/L* | 4. *Hypoxemia < 5mg/dl* |
| 5. *Serum AST > 250 IU/L* | 5. *Increased BUN > 5mg/dl* |
| | 6. *Hypoalbuminemia < 3.2 g/dl* |

***Serum amylase does not form any cirteria for prognosis in acute pancreatitis. (Remember this fact)***
***Prothrombin time is not included as an index in Ranson's criteria***

***The prognosis is best in patients where pancreatitis is caused by a remediable cause such as cholelithiasis. 'Eradication of gall stone disease' prevents further attacks of pancreatitis.*** *-Oxford text*

**Diagnosis of Acute Pancreatitis:**

**Serum Amylase**

***The diagnosis of acute pancreatitis is usually established by detection of an increased level of serum amylase. Serum amylase level is the standard laboratory test carried out to confirm the diagnosis of acute pancreatitis.***

| Measurement during first 24 hours of onset of pain | Measeurement late after presentation |
|---|---|
| An elevation of three times the upper limit of normal clinches the diagnosis (provided overt salivary gland disease and gut perforation or infarction are excluded) | After 48-72 hrs even with continuing evidence of pancreatitis, total serum levels tend to return to normal<br>With a late presentation thus, serum amylase levels may give a false negative result. |

***Serum amylase level may be increased in several other conditions***

***Remember:*** Q

There is no definitive correlation between the severity of pancreatitis and the degree of serum amylase elevation.
An elevated serum lipase Q or trypsin value is more specific / diagnostic of acute pancreatitis than serum amylase – (Lipase is the single best enzyme to measure for acute pancreatitis Q).

**Serum Lipase**

***Serum lipase elevation is the most specific laboratory test for establishing a diagnosis of Acute Pancreatitis***
*'A three fold elevated serum lipase value is usually diagnostic of acute pancreatitis' – Harrison*

*An elevated serum Lipase level is more specific for pancreatitis than a serum amylase level because many other pathologic conditions may present with an elevated amylase level. Serum lipase is therefore the single best answer of choice.*

**Purtscher's retinopathy** *is a relatively unusual complication of acute pancreatitis*. It is manifested by ***sudden and severe loss of vision***. It is believed to be due to occlusion of the posterior retinal artery with aggregated granulocytes.

**Peculiar Fundoscopic appearance :**

*Cotton wool spots and hemorrhages confined to an area limited by the optic disk and macula.* Q

## Pseudopancreatic cyst_*('pseudo' because they do not have an epithelial lining)*

- *Pseudocyst is the most common complication of acute pancreatitis usually occurring after 2-3 week*
- *Most comon cause of pancreatic pseudocyst is Pancreatitis (90%)(The second most common cause is trauma (10%))*
- *Most common site for pseudopancreatic cyst is the body and tail of pancreas*
- *The investigation of choice for Pseudopancreatic Cyst is Ultrasonography*
- *Treatment is indicated for Pseudocyst > 5cm diameter and more than 6 weeks old* Q

| *Indications for Drainage :* |
|---|
| *1. Pseudocyst > 5cm in diameter.* Q |
| *2. Persisting for > 6 weeks.* Q |

**A singnificant number of pseudocysts will resovle sponteaneously more than 6 weeks after their formations* Q

- *Initial procedure in the management of uncomplicated persistant pancreatic pseudocysts is Percutaneous aspiration*
- *Surgical internal drainage in the form of cystojejunostomy continues to be the treatment of choice.*

**Treatment of Pancreatic Psuedocyst :**

| *If the Pseudocyst is shrinking, & in stable patients who are free of complications* | *If the pseudocyst is expanding, or not responding to above treatment, or is complicated by rupture, hemorrhage or abscess formation.* |
|---|---|
| Conservative treatment is indicated.*<br>Alternatively, a USG / CT guided single or repeated needle aspiration can be done. | Operative treatment is indicative<br>Either external or preferably internal drainage of the cyst can be done |

*Percutaneous aspiration has emerged as a simple and frequently used initial procedure in the management of uncomplicated persistant pancreatic pseudocysts.* However ***it cannot be termed as the treatment of choice. Surgical internal drainage in the form of cystojejunostomy continues to be the treatment of choice.***

**Pseudopancreatic cyst:**

| **Etiology :** | **Site :** | **Diagnosis:** |
|---|---|---|
| *Pancreatitis (90%)(Most common)* Q<br>*Trauma (10%)* Q | ***85% are seen in body and tail***<br>*15% are seen in head* | *- Serum amylase level is elevated* Q<br>*- Sonography is the investigation of choice* Q<br>*- X-Ray : Pseudocysts may be localized, displacing some portion of git.* Q |
| **Complications :** | **Factors indicating possibility of hemorrhage** | |
| Pain due to expansion<br>*Haemorrhage*<br>*Rupture*<br>Abscess | Increase in size<br>*Localized brui over mass* Q<br>*Sudden decrease in Hb or hematocrit* Q | |
| **Management** | | |
| • *Pseudocyst > 5cm diameter is an indications for drainage* Q<br>• Pseudocyst *less than 5 cm* in diameter and *less than 6 weeks old should be observed* Q, as they tend to resolve spontaneously<br>• *Initial management : US/CT guided, single or repeated needle aspirations*<br>• Later : patients who do not respond to above modality are treated with surgical therapy preferred modality :<br>*Internal drainage of cyst by cystojejunostomy.* Q | | |

## Zollinger Ellison Syndrome

Zollinger Ellison Sydrome is characterized by unregulated secretion of gastrin leading to hypersecretion of gastric acid and the resulting manifestations.

**'Gastrinomas' ( non β cell tumour)** Q
↓
**Increased gastrin** Q **secretion**
↓
**Gastric acid hypersecretion** Q
↓
**Peptic ulceration** Q
(And diarrhea)

### Peptic ulceration Q

- ***Most common manifestation***, occuring in 90% of patient
- ***Most common site is duodenum (duodenal bulb)***
- **Clinical situations that raise special suspicion include :**
  a. *Ulcers beyond the duodenal bulb (second part of duodenum and beyond) because these are unusual locations for ulcers in Peptic ulcer diseases.* Q
  b. *Ulcers refractory to standard medical therapy* Q
  c. ***Ulcers are recurrent*** Q
  d. *Ulcers presenting with frank complications.* Q

### Diarrhea Q

- ***Is a common manifestation Q***
- ***Etiology is multifactorial, and it may have a secretory component*** *as well.*

**Presenting symptom in order of frequency**

- Abdominal pain (70-100%)
- Diarrhea (37-73%)
- Gastroesophageal reflux disease (GERD) (30-35 years)

### Observations in patients with peptic ulcer disease that should suggest a diagnosis of ZES

| Observation that should suggest the diagnosis |
|---|
| • *Peptic ulcer disease (PUD) with diarrhea* |
| • *PUD in an unusual location or with multiple lesions* |
| • *PUD that is refractory to treatment or persistent* |
| • *PUD that is associated with findings suggestive of MEN I* |
| • *PUD without H. pylori infection.* |

*Chronic unexplained diarrhea should also suggest gastrinoma*

### Diagnosis of Zollinger Ellison Syndrome

| | | |
|---|---|---|
| STEP I | Assess fasting gastrin level | Gastrin levels are increased |
| STEP II | Assess acid secretion : BAO estimation | BAO is increased ; BAO / MAO is increased |
| STEP III | Perform provocative test if required. | i.v. secretin induces substantial increase in serum gastrin. |

*Zollinger Elision syndrome is characterized by an increased basal gastric acid output. The ratio of BAO to MAO (maximal acid output) is increased.*

***Gastrin provocative tests*** *are used when acid secretory studies are not contributory* and include :

- *Secretin stimulation test* Q*: most sensitive and specific* Q
- Calcium infusion test
- Standard meal test

***Secretin injection test is the most valuable provocative test in identifying patients with ZES***

***Histamine stimulation is not used and it does not bring about massive release of HCl in such patients.***

### Treatment of ZES

***PPIs are the treatment of choice for Zollinger - Ellison Syndrome and have decreased the need for total gastrectomy.***

## Insulinomas

- *Insulinomas are endocrine tumors of pancreas derived from Beta cells* ectopically secrete Insulin and result in Hypoglycemia

Classic presentation of ***insulinoma*** : ***'Whipple's triad'*** [Q] : - *Harrison 14th/589*

1. *Fasting hypoglycemia* [Q]
2. *Symptoms of hypoglycemia* [Q]
3. *Immediate relief after I.V. glucose administration* [Q]

- *They are generally small (>90% < 2 cm), usually single (90%) and usually benign (only 5-15% are malignant)*
- *The most common site of Insulinomas is the Pancreas.*

**Insulinomas**

Insulinomas are Endocrine tumors of the pancreas derived from Beta cells that ectopically secrete Insulin and result in Hypoglycemia

Average age of occurrence is 40-50 years

- *Generally Small* [Q] (>90% are < 2cm)
- *Usually single* [Q] (Not multiple in 90%)
- *Usually Benign* [Q] (5-15% are malignant)
- *Invariably occur in the pancreas* [Q] (Distributed equally in pancreatic Head, Body and Tail)

**Symptoms due to Hypoglycemia**

Most common symptoms are due to the effect of hypoglycemia on the central nervous system (Neuroglycemic Symptoms)

- Confusion
- Headache
- Disorientation
- Visual difficulties
- Irrational behavior (even coma)

**Symptoms due to Excessive Catecholamine Release secondary to Hypoglycemia**

- *Sweating*
- *Tremor*
- *Palpitation*

- *Insulinoma is characterised by an increase in weight (weight gain) and not by weight loss.*
  *Weight* ***gain may result from increased food ingested to combat symptoms of hypoglycemia.***

### Diagnosis of Insulinomas

- *Diagnosis of Insulinoma requires demonstration of inappropriately high levels of plasma Insulin (and C-peptide) in the presence of documented hypoglycemia (Achieved by 72 hour fast test).*
- *Absolute values of Insulin or C- peptide are not reliable in establishing a diagnosis unless hypoglycemia is documented*
- ***The Gold standard test for diagnosis of Insulinoma is a supervised '72 hour fast' test***
  ***The '72 hour fast test' allows demonstration of hypoglycemia, together will elevated levels of Insulin and C-peptide and thus becomes the most reliable – gold standard test for establishing a diagnosis of Insulinoma***

The '72 hour fast' test involves supervised fasting for upto 72 hours or until hypoglycemia can be documented
*The test is considered positive if at any time when blood glucose levels drop to < 2.2mmol/l (40 mg/dl), the serum insulin levels are recorded to be greater than 6μU/ml. (and C- peptide levels > 100 pmol/l)*

## Pancreatic Cholera (VIPoma; 'Verner – Morrison Syndrome' or 'WDHA Syndrome')

- *Pancreatic cholera is a Pancreatic endocrine tumor, most commonly of the Delta cells, characterized by net secretion of salt and water by gut*
- Pancreatic cholera **results from excessive secretion of VIP from endocrine tumors i.e. VIPomas**

*'VIP' is an important neurotransmitter ubiquitously present in CNS and G.I. tract*
Known actions of VIP explain most features of the clinical syndrome. These include :
- Stimulation of small intestinal chloride secretion
- Effects on smooth muscle contractility
- Inhibition of acid secretion
- Vasodilatory effects

- Pancreatic cholera is synonymous with 'Verner – Morrison Syndrome' or 'WDHA Syndrome'
- *Features of Pancreatic Cholera and/or WDHA Syndrome*

**Features of Pancreatic cholera:**
- *Severe watery diarrhea* $^{\varrho}$ / flushing / weight loss
- ***Hypokalemia*** $^{\varrho}$
- ***Hypochlorhydria*** $^{\varrho}$
- ***Hypercalcemia*** $^{\varrho}$ ***(not Hypocalcemia)***
- ***Hyperglycemia*** $^{\varrho}$
- Inordinate fecal water and electrolyte loss

**WDHA Syndrome**
Watery Diarrhea
Hypokalemia
Achlorhydria

## Various Endocrinal Tumors of Pancreas:

| *Pancreatic Endocrinal Tumor* | *Biologically active Peptides secreted* |
|---|---|
| *Zollinger Ellison Syndrome* | *Gastrin* |
| *VIPoma (Verner Morrison Syndrome, Pancreatic cholera, WDHA)* | *VIP* |
| *Glucagonoma* | *Glucagon* |
| *Insulinoma* | *Insulin* |
| *Somatostatinoma* | *Somatostatin* |
| *GRFoma* | *Growth hormone releasing hormone* |
| *ACTHoma* | *ACTH* |

## QUESTIONS

### Esophageal Conditions

#### Dysphagia (General / Differential Diagnosis):

1. A 30 year old female patient presents with non progressive dysphagia, for both solids and liquids. The charachteristic finding on baruim swallow that will confirm the probable diagnosis is: *(AI 2008)*
   A. Dilated esophagus with narrow lower end (Rat tail esophagus)
   B. Multiple sacculations and pseudodiverticulae (Corkscrew esophagus)
   C. Narrow and irregular esophageal lumen
   D. Stricture ulcer in the esophagus
2. A lady presented with non progressive dysphagia only for solids. Barium study showed proximal esophageal dilatation with distal constriction. The most likely diagnosis is. *(AI 2010)*
   A. Peptic Stricture
   B. Carcinoma Esophagus
   C. Achalasia Cardia
   D. Lower Esophageal Ring
3. A 40 year old female patient with dysphagia to both liquids and solids and regurgitation for 3 months. The dysphagia was non-progressive. What is the most likely diagnosis? *(AIIMS May 2006)*
   A. Carcinoma of the esophagus
   B. Lower oesophageal mucosal ring
   C. Achalasia cardia
   D. Reflux esophageal with esophageal stricture
4. Intermittent dysphagia is caused by (select two best options): *(PGI June 04)*
   A. Stricture
   B. Achalasia cardia
   C. Pharyngeal diverticulum
   D. Diffuse esophageal spasm
5. Oesophageal motility disorder are best diagnosed by? *(NBE)*
   A. Barium studies
   B. Endoscopy
   C. 24 hour p H monitoring
   D. Manometry
6. Investigation of choice for dysphagia for solids:
   A. Barium swallow *(PGI Dec 03)*
   B. Endoscopy
   C. X-ray chest
   D. C. T. scan
7. A patient present with dysphagia of 4 weeks duration. Now he is able to swallow liquid food only. Which of the following is the one investigation to be done:
   A. Barium studies are the best to be done
   B. Upper GI endoscopy is to be done
   C. CT scan is needed *(PGI June 2000)*
   D. Esophageal manometry
8. Dysphagia lusoria is due to: *(AIIMS Nov 03)*
   A. Oesophageal diverticulum
   B. Aneurysm of aorta
   C. Oesophageal web
   D. Compression by aberrant blood vessel
9. Non progressive contraction of Esophagus are:
   A. Primary *(AI 2009)*
   B. Secondary
   C. Tertiary
   D. Quaternary

#### Achalasia Cardia

10. True about achalasia cardia is (select two best options)
    A. Dysphagia is a presenting symptom
    B. The cause is the absence of Auerbach's plexus
    C. Esophagectomy is the treatment *(PGI June 02)*
    D. Motility-improving agents are used in treatment
    E. Barium swallow shows irregular filling defect in lower esophagus
11. In achalasia cardia, true is: *(PGI June 2000)*
    A. Pressure at distal end increased with no peristalsis
    B. Low pressure at LES with no peristalsis
    C. Pressure > 50 mmHg with peristalsis
    D. Pressure at the distal end increased with normal relaxation
12. A young patient with dysphagia more for liquids than solids. He regurgitates food often at night. Radiography shows a rat tailed appearance. Likely diagnosis is : *(AIIMS May 1996)*
    A. Achlasia cardia
    B. CA oesophagus
    C. Zenker's diverticulum
    D. Diffuse esophageal spasm
13. A young patient presents with history of dysphagia more to liquid than solids. The first investigation you will do is: *(AIIMS June 03)*
    A. Barium swallow
    B. Esophagoscopy
    C. Ultrasound of the chest
    D. C.T. scan of the chest
14. Heller's operation is done for: *(AIIMS Nov 93)*
    A. Achalasia cardia
    B. Pyloric stenosis
    C. Peptic ulcer
    D. CA Esophagus

15. In which of the following cases is Heller's operation done? *(NBE)*
    A. Achalasia cardia
    B. Carcinoma esophagus
    C. Strictures of esophagus
    D. Hypertorphic pyloric stenosis

## Diffuse Esophageal Spasm

16. Diffuse esophageal spasm is best diagnosed by:
    A. Endoscopy *(AI 2008)*
    B. Manaometry
    C. Barium swallow
    D. CT
17. Corkscrew esophagus is seen in which of the following conditions? *(AI 2002)*
    A. Carcinoma esophagus
    B. Scleroderma
    C. Achalasia cardia
    D. Diffuse esophagus spasm
18. A young patient has dysphagia and symptoms of GERD. The barium swallow showed a corkscrew esophagus. What would be the MOST likely diagnosis? *(NBE)*
    A. Achalasia cardia
    B. Esophageal stricture
    C. Carcinoma esophagus
    D. Diffuse esophageal spasm
19. On barium swallow,'corkscrew esophagus' is seen in which of the following? *(NBE)*
    A. Esophagitis
    B. Achlasia cardia
    C. Carcinoma esophagus
    D. Diffuse esophageal spasm

## Zenker's Diverticulum

20. A male aged 60 years has foul breath; He regurgitates food that is eaten 3 days ago. A gurgling sound is often heard on swallowing : Likely diagnosis is: *(AI 2001)*
    A. Zenkers diverticulum
    B. Meckels diverticulum
    C. Scleroderma
    D. Achalasia cardia
21. All of the following statements about Zenker's diverticulum are true Except: *(AI 2009)*
    A. Acquired diverticulum
    B. Lateral X-rays on Barium swallow are often diagnostic
    C. False Diverticulum
    D. Out pouching of the anterior pharyngeal wall, just above the cricopharyngeus muscle.
22. A man aged 60 years presents with intermittent dysphagia & foul breath. He regurgitates food that is eaten few days ago: Likely diagnosis is:
    A. Zenker's diverticulum *(AI 91)*
    B. Meckel's diverticulum
    C. Scleroderma
    D. Achalasia cardia
23. Commonest complication of Zenker's diverticulum is: *(AIIMS Nov 96)*
    A. Dysphonia
    B. Gastroesophageal reflux
    C. Lung abscess
    D. Perforation
24. Which of the following is TURE about Zenker's diverticulum: *(AI 1995)*
    A. It is asymptomatic
    B. Occurs in the mid-esophagus
    C. Treatment is simple excision
    D. It occurs in children

## Oesophageal Ring / Web

25. Schatazki's ring is: *(PGI Dec 98)*
    A. Mucosal ring at squamous columnar junction
    B. Muscular ring
    C. Dysphagia is the presenting symptom
    D. Inflammatory stricture
26. All are true regarding Plummer Vinson syndrome, *except*: *(AIIMS Dec 97)*
    A. Oesophageal web
    B. Predisposes to malignancy
    C. Koilonchia
    D. Common in elderly males

## Barret's Esophagus

27. Barret's esophagus is diagnosed by: *(AIIMS Nov 06)*
    A. Squamous metaplasia
    B. Intestinal metaplasia
    C. Squamous dysplasia
    D. Intestinal dysplasia
28. All except one are true regarding Barret's oesophagus: *(AIIMS Feb 97)*
    A. More incidence of squamous cell carcinoma
    B. Metaplasia
    C. Columnar epithelium
    D. Involves lower oesophagus
29. Barret's esophagus can lead to: *(AIIMS June 98)*
    A. Stricture
    B. Reflux esophagitis
    C. Peptic ulcer
    D. Achalasia
30. All of the following are true about Barret's esophagus, Except: *(PGI June 03)*
    A. Consequence of prolonged GER
    B. It is premalignant

C. Lower oesophageal mucosa is replaced by intestinal type of epithelium
D. Associated with oesophageal varices
E. Predisposes to adenocarcinoma

31. False about Barret's Esophagus is: *(PGI Dec 03)*
A. Premalignant conditions
B. Can be diagnosed by seeing under endoscope
C. Biopsy is necessary to confirm diagnosis
D. Stricture may be present in high esophagus
E. None

32. What is true regarding Barret's esophagus:
A. Seen in females *(AIIMS Nov 94)*
B. Premalignant
C. Responds to conservative management
D. Squamous metaplasia is seen

33. Barret's esophagus is commonly associated with one of the following: *(AIIMS May 06)*
A. Adenocarcinoma
B. Squamous cell carcinoma
C. Sarcoma
D. Gastrointestinal stromal tumor

## Esophageal Carcinoma

34. Which of the following statements about Mallory Weiss Syndrome are true: *(PGI 2009)*
A. Presents with hemoptysis
B. Shows transmural rupture
C. Chest pain and shortness of breath
D. Shows mucosal tear

35. The most prevalent esophageal cancer world wide is:
A. Squamous cell ca *(AI 1991)*
B. Adenocarcinoma
C. Sarcoma
D. Adenoid cystic carcinoma

36. Most common site of carcinoma esophagus is:
A. Middle 1/3rd *(AIIMS Feb 97)*
B. Upper 1/3rd
C. Lower 1/3rd
D. Lower end of esophagus

37. Most common site for squamous cell carcinoma esophagus is: *(AI 01)*
A. Upper third
B. Middle third
C. Lower third
D. Gastro-esophageal junction

38. The most common site of esophageal adenocarcinoma is: *(AIIMS Nov 96, June 2000)*
A. Upper 1/3rd
B. Middle 1/3rd
C. Lower 1/3rd
D. Upper 2/3rd

39. The commonest site of carcinoma esophagus in India is: *(AIIMS Nov 03)*
A. Upper 1/3rd
B. Middle 1/3rd
C. Lower 1/3rd
D. GE Junction

40. The following are predisposing factors for Esophageal carcinoma *except* *(AI 1996)*
A. Plummer-Vinson syndrome
B. Tylosis palmaris
C. Chronic Achalasia
D. Benzene therapy

41. Hyperkeratosis of palm and sole is seen in:
A. Carcinoma colon *(AIIMS Dec 97)*
B. Hepatoma
C. Adenocarcinoma lung
D. Ca oesophagus

42. Esophageal adenocarcinoma is predisposed by (select two best options): *(PGI June 99)*
A. Achalasia
B. Scleroderma
C. Corrossive intake
D. Barrets esophagus

43. The adenocarcinoma of esophagus-develops in
A. Barret's esophagus *(AI 2002)*
B. Long standing achalasia
C. Corrosive structure
D. Alcohol abuse

44. Adenocarcinoma of esophagus is commonly found in
A. Achlasia acardia *(AI 1998)*
B. Barret's oesophagus
C. Plummer vinson syndrome
D. Chronic smoking

45. All of the following statements about Esophageal carcinoma are true, Except: *(PGI June 98, Dec 03)*
A. More common in Men
B. Adenocarcioma is on rise
C. Most common in elderly
D. Dysphagia is most common symptom
E. Pernicious anemia is a risk factor

46. Which neo-adjuvant chemotherapy is used in Esophageal carcinoma *(AI 1996)*
A. Cisplatin
B. Cyclophosphamide
C. Doxorubicin
D. Methotrexate

47. The commonest side effect of cisplatinum in a patient using it for esophageal carcinoma is :
A. Acute tubular necrosis
B. Thrombocytopenia *(AIIMS May 01)*
C. Hepatic failure
D. Cardiomyopathy

48. Best substitute of esophagus after esophagectomy is:
A. Stomach *(AI 1996)*
B. Jejunum
C. Left colon
D. Right colon

## Stomach and Duodenum

### Peptic Ulcer Disease & H. Pylori Infection

49. Peptic ulcer is associated with all except one:
    A. Cirrhosis *(AIIMS Feb 1997)*
    B. Zollinger Ellisons syndrome
    C. Primary hyperparathyroidism
    D. Pernicious anemia
50. Which one is not associated with peptic ulcer:
    A. Smoking cigarette *(AIIMS Nov 95)*
    B. Zollinger Ellison syndrome
    C. Plummer Vinsons syndrome
    D. Cirrhosis
51. All of the following are associated with Gastric Ulcer's Except: *(AI 1992)*
    A. H. Pylori infection
    B. High Acid output
    C. Smoking
    D. Bile Reflux
52. Stress ulcers seen in burns are: *(PGI Dec 2000)*
    A. Curling's ulcer
    B. Cushing's ulcer
    C. Meleney's ulcer
    D. Rodent ulcer
53. Helicobacter pylori is not associated with :
    A. Gastrointestinal lymphoma *(AIIMS Nov 03)*
    B. Gastric cancer
    C. Gastric leiomyoma
    D. Peptic ulcer
54. Endoscopic biopsy from a case of H.pylori related duodenal ulcer is most likely to reveal :
    A. Antral predominant gastritis *(AIIMS Nov. 04)*
    B. Multifocal atrophic gastritis
    C. Acute erosive gastritis
    D. Gastric atrophy
55. H. pylori is known to cause all of the following *except*: *(AI 1999)*
    A. Gastric ulcer
    B. Duodenal ulcer
    C. Gastric lymphoma
    D. Fundal atrophic gastritis
56. Diagnostic tests for H. Pylori include all of the following ***except*** : *(AI 1999)*
    A. Urea-breath test
    B. Rapid urease test
    C. Gastric biopsy & Warthin-starry stain
    D. SAFA test
57. Epidemiological studies of H. pylori are done by using: *(AI 1999)*
    A. Urea-breath test
    B. Serological markers
    C. Culture
    D. Gastric-biopsy urease test
58. Which of the following is False regarding H.Pylori infection : *(AIIMS June 2000)*
    A. With chronic infection urease breath test become negative
    B. H.Pylori infection remain lifelong if untreated
    C. Endoscopy is diagnostic
    D. Toxigenic strains usually causes ulcer
59. A patient with H. Pylori infection is treated with drugs. The best method to detect presence of residual H.Pylori infection in this person is : *(AI 2007)*
    A. Rapid unrease test
    B. Urea breath test
    C. Endoscopy and biopsy
    D. Serum anti H.Pylori titre
60. The preferred test for confirming H. pylori eradication is: *(NBE)*
    A. Urease breath test
    B. Culture
    C. Serological test
    D. Biopsy urease test
61. All are true regarding Helicobacter pylori ***except***:
    A. Less prevalent in developing countries
    B. Toxicogenic strains usually causes ulcers
    C. Urea breath test is positive *(AIIMS Feb 97)*
    D. Gram negative organism
62. Which of the following statements about peptic ulcer disease is true : *(AIIMS May 03)*
    A. Helicobacter pylori eradication increases the likelihood of occurrence of complications.
    B. The incidence of complications has remained unchanged
    C. The incidence of Helicobacter pylori reinfection in India is very low.
    D. Helicobacter pylori eradication does not alter the recurrence ratio.
63. Which drug is ***not*** effective against H. pylori:
    A. Colloidal Bismuth *(AI 1995)*
    B. Metronidazole
    C. Amoxicillin
    D. Erythromycin
64. All of the following are used for treatment of H.Pylori, except: *(NBE)*
    A. Gentamycin
    B. Clarithromycin
    C. Metronidazole
    D. Amoxicillin
65. All of the following drugs are commonly used in regimens against H. pylori except: *(AI 2008)*
    A. Oxytetracycline
    B. Amoxicillin
    C. Bismuth Subcitrate
    D. Omeprazole
66. All are used in treatment of Helicobactor pylori, EXCEPT: *(AIIMS Dec 97)*
    A. Colloid bismuth

B. Cisapride
C. Clarithromycin
D. Metronidazole

67. Common sites for Cushing ulcers include all of the following *except* : *(AI 1999)*
A. Esophagus
B. Stomach
C. 1st part of duodenum
D. Distal duodenum

68. Commonest site of peptic ulcer is : *(AI 1999)*
A. Ist part of Duodenum
B. IInd part of duodenum
C. Distal 1/3 of stomach
D. Pylorus of the stomach

69. The most common site of a benign (peptic) gastric ulcer is: *(AIIMS June 04)*
A. Upper third of lesser curvature
B. Greater curvature
C. Pyloric antrum
D. Lesser curvature near incisura angularis

70. Most common complication of chronic gastric ulcer is: *(AIIMS June 93)*
A. Tea pot stomach
B. Scirrhous carcinoma (adenocarcinoma)
C. Perforation
D. Haemorrhage

71. Artery to bleed in duodenal ulcer haemorrhage:
A. Splenic artery *(PGI Dec 2000)*
B. Gastroduidenal artery
C. Left gastric artery
D. Superior mesenteric artery

72. A posteriorly perforating ulcer in the pyloric antrum of the stomach is most likely to produce initial localized peritonitis or abscess formation in the following: *(AI 2003)*
A. Omental bursa (lesser sac)
B. Greater sac
C. Right subphrenic space
D. Hepato renal space (pouch of Morison)

73. All of the following are true regarding a patient with acid peptic disease *except* *(AI 2001)*
A. Misoprostol is the drug of choice in patients on NSAIDS
B. DU is preventable by the use of single night time H2 blockers
C. Omeprazole may help ulcers refractory to H2 blockers
D. Misoprostol is DOC in pregnant patients

74. Surgery of choice for chronic duodenal ulcer is:
A. Vagotomy + antrectomy *(AIIMS June 93)*
B. Total gastrectomy
C. Truncal vagotomy + pyloroplasty
D. Highly selective vagotomy

75. Patient presents with recurrent duodenal ulcer of 2.5 cm size; procedure of choice *(AI 2001)*
A. Truncal vagotomy and antrectomy
B. Truncal vagotomy and gastrojejunostomy
C. Highly selective vagotomy
D. Laparoscopic vagotomy and gastrojejunostomy

76. The lowest recurrence of peptic ulcer is associated with *(AI 2002)*
A. Gastric resection
B. Vagotomy + drainage
C. Vagotomy + Antrectomy
D. Highly selective vagotomy

77. Dumping syndrome is due to: *(AI 1999)*
A. Diarrhoea
B. Presence of hypertonic content in small intestine
C. Vagotomy
D. Reduced gastric capacity

78. All are true regarding Early Post-cibal syndrome, except: *(AI 2000)*
A. Distension of abdomen
B. Managed conservatively
C. Hypermotility of intestine is common
D. Surgery is usually indicated

## Gastric Outlet Obstruction

79. In gastric outlet obstruction in a peptic ulcer patient, the site of obstruction is most likely to be : *(AI 2002)*
A. Antrum
B. Duodenum
C. Pylorus
D. Pyloric canal

80. What is the most characteristic of congenital hypertrophic pyloric stenosis: *(AI 2003)*
A. Affects the first born female child
B. The pyloric tumour is best felt during feeding
C. The patient is commonly marasmic
D. Loss of appetite occurs early

81. What is true regarding congenital hypertrophic pyloric stenosis : *(AI 2001)*
A. More common in girls
B. Hypochloremic alkalosis
C. Hellers myotomy is the procedure of choice.
D. Most often manifests at birth

82. In a case of hypertrophic pyloric stenosis, the metabolic disturbance is *(AI 2002)*
A. Respiratory alkalosis
B. Metabolic acidosis
C. Metabolic alkalosis with paradoxical aciduria
D. Metabolic alkalosis with alkaline urine

83. Metabolic changes associated with excessive vomitting includes the following: *(AI 1999)*
A. Metabolic acidosis
B. Hyperchloremia
C. Hypokalemia
D. Decreases bicarbonates

84. Patient with pyloric stenosis secondary to peptic ulcer, complains of profuse vomiting and $Na^+$ - 125meq/L, $K^+$ --> 2.3 meq/L and $Cl^-$ --> 85 meq/L, BE-8meq/L should be given. *(AIIMS June 2000)*

A. Half normal saline
B. Normal saline
C. $K_+$ bolus
D. Hypertonic saline

85. For which of the following is the Ramstedt's operation done? *(NBE)*
A. Ileal atresia.
B. Achalasisa cardia
C. Hirschsprung's disease
D. Hypertrophic pyloric stenosis of infancy

86. The MOST frequent indication for Nissen fundoplication operation is: *(NBE)*
A. GERD.
B. Barrett's esophagus
C. Mallory-weiss syndrome.
D. Achalasia of esophagus.

**Menetrier's disease**

87. All are true regarding Menetrier's disease, EXCEPT:
A. Protein loss *(AIIMS Dec 94)*
B. Exophytic growth
C. Hypertrophy of gastric mucosa
D. Premalignant condition

88. All of the following statements about Menetrier's disease are true Except: *(NBE)*
A. It is a premalignant condition
B. Usually increased acid secretion
C. May be confused with Zollinger Ellison Syndrome
D. Associated with Protein losing enteropathy

**Carcinoma Stomach**

89. Risk factor for development of gastric Ca :
A. Blood group O *(AI 2002)*
B. Duodenal ulcer
C. Intestinal hyperplasia
D. Intestinal metaplasia type III

90. Premalignant conditions of stomach include all, Except: *(NBE)*
A. Gastric ulcer
B. Pernicious anemia and achlorhydria
C. Hiatus Hernia
D. Atrophic gastritis

91. Predisposing cause for carcinoma stomach are except:
A. Chronic gastric atrophy *(PGI Dec 97)*
B. Hyperplastic polyp
C. Intestinal Metaplasia grade III
D. Pernicious anemia

92. Risk factor for carcinoma stomach include all of the following, Except: *(PGI June 2000)*
A. Blood group A
B. Atrophic Gastrititis
C. Duodenal Peptic ulcer
D. Partial Gastrectomy

93. Which one of the following is the most significant risk factor for development of gastric carcinoma?
A. Paneth cell metaplasia *(AI 2006)*
B. Pyloric metaplasia
C. Intestinal metaplasia
D. Ciliated metaplasia

94. Most common site for carcinoma stomach is:
A. Antrum *(AIIMS June 93)*
B. Fundus
C. Lesser curvature
D. Greater curvature

95. When carcinoma of stomach develops secondarily to pernicious anemia, it is usually situated in the:
A. Prepyloric region *(AI 2006)*
B. Pylorus
C. Body
D. Fundus

96. Early gastric cancer generally indicates :
A. Gastric adencarcinoma detected early
B. Gastric adenocarcinoma confined to the mucosa
C. Gastric adenocarcinoma confined to the mucosa & submucosa *(AIIMS May 1996)*
D. Gastric adenocarcinoma less than 1 cm. In size

97. All the following indicates early gastric cancer ***except***
A. Involvement of mucosa *(AI 2002)*
B. Involvement of mucosa and submucosa
C. Involvement of mucosa, submucosa and muscularis
D. Involvement of mucosa, submucosa and adjacent lymph nodes

98. The best prognosis in carcinoma stomach is with:
A. Superficial spreading type *(AI 1995)*
B. Ulcerative type
C. Linitis plastica type
D. Polypoidal fungating type

99. An adult presented with hemetemesis and upper abdominal pain. Endoscopy revealed a growth at the pyloric antrum of the stomach. CT scan showed growth involving the pyloric antrum without infiltration or invasion into surrounding structures and no evidence of distant metastasis. At Laparotomy neoplastic growth was observed to involve the posterior wall of stomach and the pancreas extending 6cm up to tail of pancreas. What will be the most appropriate surgical management: *(AI 2010)*
A. Closure of the abdomen
B. Antrectomy and vagotomy
C. Partial Gastrectomy + Distal pancreatectomy
D. Partial Gastrectomy + Distal pancreatectomy + splenectomy

100. Amongst the following, the most common site for Leiomyoma is *(AI 1994)*
A. Stomach
B. Small Intestine
C. Duodenum
D. Colon

## Malabsorption Syndrome and Disorders of Small Intestine

### General

101. Which of the following is not a malabsorption syndrome: *(NBE)*
   A. Whipple's disease
   B. Coeliac disease
   C. Tropical sprue
   D. Tangier's disease

102. Non absorbtion of fat soluble vitamins is due to: *(NBE)*
   A. Steatorrhea
   B. Pancreatic endocrine insufficiency
   C. Both
   D. None

103. Test for assessment of mucosal function of GIT: *(AI 2009)*
   A. D-xylose test
   B. Small bowel study
   C. Biopsy
   D. Schilling test

104. Positive D – xylose test indicates all of the following, Except: *(AI 1992)*
   A. Pancreatic insufficiency
   B. Small intestinal mucosal disease
   C. Impaired carbohydrate absorption in small intestine
   D. Malabsorption

105. A 41 year old patient presented with chronic diarrhoea for 3 months. A d-xylose absorption test was ordered to look for: *(AIIMS Nov 02)*
   A. Carbohydrate malabsorption due to mucosal disease.
   B. Carbohydrate malabsorption due to chronic pancreatitis
   C. Fat malabsorption due to mucosal disease.
   D. Fat malabsorption due to chronic pancreatitis.

106. Best test for Small intestine malabsorption of carbohydrates is : *(AI 1997)*
   A. Lund meal test :
   B. Shilling test
   C. D-Xylose test
   D. Follacin test

107. A d-xylose test was requested on a patient with history of long standing steatorrhea '5' hour urine sample showed <4.0 gm excretion after giving 25 gm of d-xylose. The most likely diagnosis is : *(PGI 09)*
   A. Chronic Pancreatitis
   B. Bacterial overgrowth syndrome
   C. Ileal disease
   D. Celiac sprue
   E. Intestinal Lymphangiectasia

108. Cause of False positive D-xylose test include all of the following, Except *(PGI 01)*
   A. Bacterial overgrowth
   B. Renal failure
   C. Ascitis
   D. Celiac sprue
   E. Blind loop syndrome

109. False positive D-xylose test may be seen in
   A. Blind loop syndrome *(PGI June 01)*
   B. Ascitis
   C. Antibiotic therapy
   D. Pyloric stenosis
   E. All of the above

110. Which of the following statements about Schilling's test are true: *(PGI 2009)*
   A. Abnormal in pernicious anemia
   B. Normal in bacterial overgrowth syndrome
   C. Abnormal in ileal disease
   D. Normal in chronic pancreatitis

111. Which of the following is not used for investigation of fat malabsorption: *(NBE)*
   A. 13C Trioctanoin
   B. 13C Triolein
   C. 13C Tripalmitin
   D. 13C Triclosan

112. Schilling test is Abnormal in: *(NBE)*
   A. Intrinsic factor deficiency
   B. Amylase deficiency
   C. Lipase deficiency
   D. Pancreatic endocrine insufficiency

113. Which of the following statements regarding the schilling test for vitamin $B_{12}$ malabsorption is most accurate? *(NBE)*
   A. The schilling test results are abnormal in patients with dietary vitamin $B_{12}$ deficiency.
   B. In patients with pernicious anemia, the results of the schilling test normalize after oral administration of intrinsic factor,
   C. In patients with ileal disease, the results of the schilling test normalize after oral administration of intrinsic factor.
   D. Pancreatic exocrine insufficiency does not cause schilling test results to be abnormal.

114. A 12 year old girl has history of recurrent bulky stolls and abdominal pain since 3 year of age. She has moderate pallor and her weight and height are below the 3rd percentile. Which of the following is the most appropriate investigation to make a specific diagnosis? *(AI India/AIIMS)*
   A. Small intestinal biopsy
   B. Barium studies
   C. 24-hr- fecal fat estimation
   D. Urinary d-xylose test

115. Serum amylase level is raised in all except:
    A. Blocked salivary duct *(PGI June 98)*
    B. Ruptured ectopic
    C. Appendicitis
    D. Pancreatitis

## Celiac Disease

116. A 30 year old lady presents with features of malabsorption and iron deficiency anaemia. Duodenal biopsy shows complete villous atrophy. Which of the following antibodies is likely to be present :
    A. Antiendomysial antibodies *(AIIMS Nov. 05)*
    B. Anti-goblet cell antibodies
    C. Anti-saccharomyces cerevisae antibodies
    D. Antineutrophil cytoplasmic antibodies

117. Cause of thick pancreatic secretions in cystic fibrosis? *(NBE)*
    A. Overproduction of mucin
    B. Failure to clear mucin due to epithelial dysfunction
    C. Defect in chloride channel leading to water reabsorption
    D. Defect tin sodium channel leading to water reabsorption

118. 30 year male with chronic diarrhoea, anemia, raised liver enzymes. Most likely associated with:
    A. Antimitochondrial antibody *(AIIMS May 07)*
    B. Anti-endomysial antibody
    C. Anti-smooth muscle antibody
    D. Antinuclear antibody

119. A patient presents with chronic small bowel diarrhea, duodenal biopsy shows villous atrophy. Anti endomysial antibodies and IgA TTG antibodies are positive. What is the treatment of choice?
    A. Gluten free diet *(AI 2007)*
    B. Antibiotics
    C. Loperamide
    D. 5-ASA

120. Which of the following circulating antibodies has the best sensitivity and specificity for the diagnosis of celiac disease? *(AIIMS May 06)*
    A. Anti-endomysial antibody
    B. Anti-tissue transglutaminase antibody
    C. Anti-gliadin antibody
    D. Anti-reticulin antibody

121. The histological features of coeliac disease include all of the following, ***except*** : *(AI 2002)*
    A. Crypt hyperplasia
    B. Increase in thickness of the mucosa
    C. Increase in intraepithelial lymphocytes
    D. Increase in inflammatory cells in lamina propyria

122. Biopsy findings of celiac disease all of the following, except (Select two best options) : *(PGI 09)*
    A. Crypt hyperplasia
    B. Villous atrophy
    C. Mucosal atrophy
    D. Intraepithelial lymphocytes
    E. Presence of Giardia lambia

123. Proved association of celiac sprue is with:
    A. Dermatitis herpetiformis *(PGI Dec 2000)*
    B. Scleroderma
    C. Pemphigus
    D. Pemphoid

124. Celiac disease associated with: *(PGI Dec 06)*
    A. Dermatitis herpetiformis
    B. Type I DM
    C. Lymphoma
    D. Atrophic gastritis
    E. All of the above

125. Celiac sprue diagnosed by (select two options):
    A. Intestinal biopsy *(PGI Dec 02)*
    B. Unequivocal response to gluten restriction
    C. Finding of organism
    D. Improvement on dapsone treatment
    E. H/O fat malabsorption

126. Which of the following grains can be used safely in patients with celiac sprue: *(PGI Dec 01)*
    A. Rice
    B. Wheat
    C. Rye
    D. Barley

127. What a patient with gluten hypersensitivity can consume (select two best options): *(PGI Dec 06)*
    A. Rice
    B. Barley
    C. Oat
    D. Corn
    E. Rye

128. Which of the following vitamin deficiencies is uncommon in celiac disease *(NBE)*
    A. Vitamin D
    B. Folic Acid
    C. Vitamin A
    D. Vitamin $B_{12}$

## Whipple's Disease

129. In which of the following conditions of malabsorption, an intestinal biopsy is diagnostic-:
    A. Celiac disease *(AIIMS May 05)*
    B. Tropical sprue
    C. Whipple's disease
    D. Lactose intolerance

130. Macrophages containing large quantities of undigested and partial digested bacteria in intestine are seen in *(AI 2002)*
    A. Whipple's disease
    B. Amyloidosis
    C. Immunoapproliferative small instetinal disease
    D. Vibro cholerae infection

131. Histopathological findings in Whipple's disease include all of the following Except: *(AI 2008)*
   A. Marked increase in the number of macrophages in the mucosa
   B. Marked increase in the number of intraepethelial lymphocytes
   C. Dilatation of Lymphatics in the mucosa
   D. Lipid deposition in the mucosa

132. Most common CNS manifestation of Whipple's disease is : *(AI 1999)*
   A. Cerebellar ataxia
   B. Supranuclear ophthalmoplegia
   C. Seizure
   D. Dementia

133. Which of the following condition causing malabsorption has no effect on villus architecture and no inflammatory reaction? *(NBE)*
   A. Giardiasis
   B. Crohn's
   C. Whipple's
   D. Abetalipoprotienemia

134. Which of the following condition causing malabsorption has no effect on villus architecture and no inflammatory reaction? *(NBE)*
   A. Giardiasis
   B. Crohn's
   C. Whipple's
   D. Celiac Sprue

135. Which of the following parastitic infestation can lead to malabsorption syndrome? *(AI 06)*
   A. Amoebiasis
   B. Ascariasis
   C. Hookworm infestation
   D. Giardiasis

### Short Bowel Syndrome

136. The short bowel syndrome is characterized by all of the following *except* : *(AI 2004)*
   A. Diarrhea
   B. Hypogastrinemia
   C. Weight loss
   D. Steatorrhoea

137. All are complication of ileal resection, *except* :
   B. Megaloblastic anaemia *(AIIMS June 97)*
   C. Iron deficiency anaemia
   D. Gastric hypersecretion
   E. Malabsorption syndrome

138. Deficiency of which of the following vitamin is most commonly seen in short bowel syndrome with ileal resection: *(AI 2012)*
   A. Vitamin B12 (Cyanocobalamine)
   B. Vitamin B1 (Thiamine)
   C. Folic Acid
   D. Vitamin K

139. Which of the following vitamin deficiencies is most commonly seen in short bowel syndrome: *(AI 2012)*
   A. Vitamin B12
   B. Biotin
   C. Vitamin B1
   D. Vitamin K

### Intestinal Angina

140. "Intestinal angina" is a symptom complex of the following: *(AIIMS May 06)*
   A. Postprandial abdominal pain, weight loss, acute mesenteric vessel occlusion
   B. Postprandial abdominal pain, weight loss, chronic mesenteric vessel occlusion
   C. Pre-prandial abdominal pain, weight loss, chronic mesenteric vessel occlusion
   D. Pre-prandial abdominal pain, weight gain acute mesenteric vessel occlusion

## Inflammatory Bowel Disease

### Ulcerative Colitis

141. A 20 year old male presents with mucus and repeated gastrointestinal bleeding. Patient is positive for ANCA. The most likely diagnosis is: *(NBE)*
   A. Ulcerative colitis
   B. Crohn's disease
   C. Radiation colitis
   D. Ischemic bowel disease

142. A 25 year old male presents with a history of chronic diarrhea. Pathological examination reveals cryptitis and crypt abscesses. The likely diagnosis is: *(AI 2008)*
   A. Crohn's disease
   B. Ulcerative colitis
   C. Giardiasis
   D. Microscipic colitis

143. Toxic megacolon is most commonly associated with
   A. Ulcerative colitis *(AI 1996)*
   B. Crohn's disease
   C. Whipple's disease
   D. Reiter's disease

144. Pseudopolyps are features of *(AI 1994)*
   A. Crohn's disease
   B. Ulcerative colitis
   C. Celiac sprue
   D. Whipple's disease

145. Pseudopolyps are typically seen in:
   A. Crohn's disease *(NBE)*
   B. Ulcerative colitis
   C. Celiac disease
   D. Tropical sprue

146. Which of the following is MOST commonly affected by ulcerative colitis? *(NBE)*
   A. Cecum

B. Rectum
C. Sigmoid colon
D. Terminal Ileum

147. Backwash Ileitis is seen in: *(NBE)*
A. Ulcerative Colitis
B. Crohn's Disease
C. Colonic Carcinoma
D. Ileal Polyp

148. What is drug of choice for ulcerative colitis :
A. Salazopyrine *(AIIMS May 95)*
B. Pedinisolone *(AIIMS Feb 97)*
C. Mercaptopurine
D. 5-amino salicylic acid

149. All of the following drugs may be used in the treatment of ulcerative colitis Except: *(NBE)*
A. Corticosteroids
B. Azathioprine
C. Sulfasalazine
D. Methotrexate

150. A 41 year old male patient presented with recurrent episodes of bloody diarrhea & mucus for 5 years. Despite regular treatment with adequate doses of sulfasalazine, he has had several exacerbations of his disease and required several weeks of steroids for the control for flares. What should be the next line of treatment for him? *(AIIMS Nov 03)*
A. Methotrexate
B. Azathioprine
C. Cyclosporine
D. Cyclophosphamide

151. Drug effective in ulcerative colitis is: *(AIIMS Feb 97)*
A. 5 amino salicyclic acid (5-ASA)
B. Steroids
C. Salazopyrin
D. Antibiotics

## Crohn's Disease

152. Skip granulomatous lesions are seen in : *(AI 1996)*
A. Ulcerative colitis
B. Crohn's disease
C. Whipple's disease
D. Reiter's disease

153. A patient gives chronic history of Diarrhoea and blood in stool presents with multiple fistulae in the perineum and multiple stricture in small intestine. The diagnosis is: *(AIIMS June 2000)*
A. Crohn's disease
B. Radiation enteritis
C. Ulcerative Colitis
D. Ischemic bowel disease

154. Which of the following is MOST commonly affected by Crohn's Disease? *(NBE)*
A. Cecum
B. Rectum
C. Sigmoid colon
D. Terminal Ileum

155. The presence of anti-*Saccharomyces cerevisae* antibody is a surrogate marker of one of the following: *(AI 2006)*
A. Celiac disease
B. Crohn's disease
C. Ulcerative colitis
D. Tropical sprue

156. Crohn's disease may be caused by which one of the following infectious agents: *(AI 2008)*
A. Clostridium difficle
B. Mycobacterium paratuberculosis
C. Cytomegalo virus (CMV)
D. Mycoplasma

157. Extraintestinal manifestations of Inflammatory bowel disease include all of the following, Except:
A. Uveitis *(PGI June 05)*
B. Sclerosing cholangitis
C. Osteoarthritis
D. Skin nodules

158. A 25 yrs women presents with bloody diarrhea & is diagnosed as a case of Ulcerative colitis. Which of the following condition is not associated : *(AI 2002)*
A. Sclerosing cholengitis
B. Iritis
C. Ankylosing spondylitis
D. Pancreatitis

159. Antibody shown to be useful for Crohn's Disease is: *(NBE)*
A. Omalizumab
B. Palivizumab
C. Natalizumab
D. None of the above

# Colonic Disorders

## Irritable Bowel Syndrome (IBS)

160. Which one of the following is *not* a feature of irritable bowel syndrome? *(AIIMS May 05)*
A. Abdominal pain
B. Constipation
C. Rectal bleeding
D. Bloating

161. Which of the following features are associated with Irritable Bowel Syndrome: *(AI 1992)*
A. Weight loss
B. Anorexia
C. Abdominal distension
D. Blood in stool

162. A young girl presents with abdominal pain and a recent change in bowel habit, with passage of mucus in stool. There is no associated blood in stool and symptoms are increased with stress. The most likely diagnosis is. *(AI 2010)*
A. Irritable bowel syndrome

B. Ulcerative Colitis
C. Crohn's disease
D. Amebiasis

163. All of the following statements about Irritable Bowel syndrome are true, except: *(PGI)*
A. Associated with anxiety
B. Stress predisposes
C. Constipation
D. Diarrhea
E. Predisposes to malignancy in long term

164. Which of the following drugs is used for Irritable Bowel Syndrome of the constipating type: *(AI 2012)*
A. Lubiprostone
B. Cholestyramine
C. Alosetron
D. Rifaximin

## Diarrhea and Colitis

165. Which of the following organism does not cause invasive diarrhea *(NBE)*
A. Bacillus cereus
B. Aeromonas sp
C. Rota virus
D. Shigella

166. Drugs and toxins that increase the c AMP content of the intestinal mucosa cause diarrhea because they *(NBE)*
A. Increase K+ secretion in the colon.
B. Increase Cl⁻ secretion into the intestine.
C. Increase Na+ absorption in the small intestine
D. Increase Na+k+ cotransport in the small intestine

167. Secretory Diarrhea is caused by all of the following, Except: *(PGI June 07)*
A. Cholera
B. Laxatives
C. Excess phenolphthalein intake
D. Clostridium difficle

168. Secretory diarrhea is not seen in: *(NBE)*
A. Phenolphthalein
B. Celiac disease
C. Cholera
D. Addison's Disease

169. All of the following are true about Osmotic Diarrhea, except: *(NBE)*
A. Stool volume < 1 L/day
B. Diarrhea stops after fasting
C. Osmolar gap < 50
D. All of the following

170. Large bowel Colonic Diarrhoea is associated with all of the following, except: *(NBE)*
A. Large Volume Stool
B. Urgency
C. Tenesmus
D. Mucus

171. Diarrhea with acanthocytosis is seen in: *(NBE)*
A. Whipple's disease
B. Celiac sprue
C. Abetalipoproteinemia
D. Ulcerative colitis

172. Diarrhea with acanthocytosis is seen in: *(NBE)*
A. Whipple's disease
B. Celiac sprue
C. Wolman's Disease
D. Ulcerative colitis

173. Features of secretory diarrhea include all of the following, Except: *(AI 2009)*
A. Stool volume > 1D /day
B. Normal osmotic anion gap
C. Reduces with fasting
D. Painless

174. Indications for use of antibiotics in acute diarrhea include (select three options): *(PGI June 07)*
A. Febrile dysentery with fever ≥ 38.5
B. Immunocompromised patient
C. Elderly patient
D. Dehydration

175. A patient presents with severe colitis associated with an overgrowth of clostridium difficile in the lower part of intestine. Which of the following is the most likely cause of this condition? *(NBE)*
A. Stomach ulcer
B. Food poisoning
C. Antibiotic therapy
D. Immunosuppressed person

176. Pseudomembraneous colitis is caused by:
A. Clostridium welchii *(NBE)*
B. Clostridium difficile.
C. Yersinia enterocolitica.
D. Pseudomonas aeruginosa.

177. The first antibiotic linked to antibiotic associated pseudomembranous colitis is: *(NBE)*
A. Clindamycin
B. Cephalosporins
C. Vancomycin
D. Metranidazole

178. What is the MOST common cause of Traveler's Diarrhea? *(NBE)*
A. Enteroinvasive E. coli
B. Enterotoxigenic E. Coli
C. Enteropathogenic E. coli
D. Enterohemorrhagic E. coli.

179. A 14-year-old girl with history of prolonged fever and abdominal discomfort is observed to have splenomegaly and leucopenia. In the course of the disease she develops acute abdominal event and died. Which of the following is the likely finding on autopsy: *(AI 2012)*
A. Transverse ulcers
B. Longitudinal ulcers

C. Pinpoint ulcers
D. Pseudopolyps

180. A patient present with lower gastrointestinal bleed. Sigmoidoscopy shows ulcers in the sigmoid. Biopsy from this area shows flask-shaped ulcers. Which of the following is the most appropriate treatment :
A. Intravenous ceftriaxone *(AIIMS Nov. 05)*
B. Intravenous mentronidazole
C. Intravenous steroids and sulphasalazine
D. Hydrocortscone enemas

181. Investigation of choice for invasive amebiasis is:
A. Indirect heamagglutination *(AI 02)*
B. ELISA
C. Counter immune electrophoresis
D. Microscopy

182. Features of Typhoid Ulcers include all of the following Except: *(NBE)*
A. Bleeding
B. Perforation
C. Stricture and obstruction
D. Longitudinal orientation

183. A patient with leukemia on chemotherapy develops acute right lower abdominal pain associated with anemia, thrombocytopenia and leukopenia. Which of following is the clinical diagnosis? *(AI 2006)*
A. Appendictis
B. Leukemic colitis
C. Perforation peritonitis
D. Neutropenic colitis

## Colorectal Carcinomas

184. The most pre-cancerous condition for carcinoma colon is *(AI 1995)*
A. Familial polyposis
B. Hamartomatous polyps
C. Juvenile polyps
D. Hyperplastic polyps

185. Strong correlation with colorectal cancer is seen in:
A. Peutz-Jegher's polyp *(AI 2003)*
B. Familial polyposis coli.
C. Juvenile polyposis
D. Hyperplastic polyp.

186. Strong correlation with colorectal cancer is seen in:
A. Hyperplastic polyp *(NBE)*
B. Juvenile polyposis
C. Peutz-jeghers polyp
D. Familial polyposis coli

187. Which of the following colonic polyps is not pre-malignant? *(AI 2006)*
A. Juvenile polyps
B. Hamartomatous polyps associated with Peutz-Jeghers Syndrome
C. Villous adenomas
D. Tubular adenomas

188. Which one of the following conditions commonly predisposes to Colonic carcinoma? *(AI 2005)*
A. Ulcerative colitis.
B. Crohn's disease.
C. Diverticular disease.
D. Ischaemic colitis.

189. A 25-year old male had pigmented macules over the palm, sole and oral mucosa. He also had anemia and pain in abdomen. The most probable diagnosis is:
A. Albright's syndrome *(AIIMS May 05)*
B. Cushing's syndrome
C. Peutz-Jegher's syndrome
D. Incontinentia pigmenti

190. A patient presents with malena, hyperpigmentation over lips, oral mucosa and skin; and his sister is also having similar complaints. The diagnosis is :
A. Peutz Jegher's Syndrome *(AI 2000)*
B. Familial Adenomatous Polyposis
C. Gardner's Syndrome
D. Villous Adenoma

191. In Peutz-Jeghers syndrome, polyps are seen in
A. Colon *(AI 1995)*
B. Rectum
C. Small bowel
D. Stomach

192. A girl presents with complaints of malena. On examination there are pigmented lesions involving her mouth and lips. Two of her sisters also had similar complaints. Which of the following is the most probable diagnosis: *(AIIMS Nov 2000)*
A. Kornkhite Canada syndrome
B. Puetz Jegher's syndrome
C. Gardner's syndrome
D. Turcot's syndrome

193. A 25-year-old man presents to the emergency room with a history of rectal bleeding. On examination he is noted to have several epidermoid cysts and palpable bone osteomas of the mandible. Which of the following syndromes BEST describes the findings? *(NBE)*
A. Cowden's syndrome
B. Gardner's syndrome
C. Muir-Torre syndrome
D. Turcot's Syndrome

194. Most important prognostic factor for colorectal carcinoma is : *(AI 2009)*
A. Site of lesion
B. Stage of lesion
C. Age of patient
D. Lymph node status

195. After undergoing surgery, for Carcinoma of colon a patient developed single liver metastatis of 2cm. What you do next : *(AI 2002)*
A. Resection
B. Chemo radiation

C. Acetic acid injection
D. Radio frequency ablation

196. A patient was operated for colonic carcinoma and later a solitary nodule was found in the liver Treatment of choice is : *(AI 1998)*
A. Surgery
B. Radiation
C. Chemotherapy
D. Conservative treatment

197. A 50-year old male, working as a hotel cook, has four dependent family members. He has been diagnosed with an early stage squamous cell cancer of anal canal. He has more than 60% chances of cure. The best treatment option is:
A. Abdomino-perineal resection *(AI 2003)*
B. Combined surgery and radiotherapy
C. Combined chemotherapy and radiotherapy
D. Chemotherapy alone

198. All of the following genetic syndromes associated with colorectal cancer are caused by mutations on th APC gene, except: *(NBE)*
A. Lynch Syndrome
B. FAP
C. Gardner's Syndrome
D. Turcot's Syndrome

199. Lynch syndrome is an autosomal dominant disorder with an increased risk of colorectal cancer that is specifically caused by defects in: *(NBE)*
A. RB gene.
B. P53 gene.
C. WT1 gene.
D. Mismatch genes

200. All of the following genes may be involved in development of carcinoma of colon Except: *(AI 2009)*
A. APC
B. Beta – Catenin
C. K- ras
D. Mismatch Repair Genes

201. Based on Epidemiological studies, which of the following has been found to be most protective against Carcinoma Colon : *(AI 2009)*
A. High fiber diet
B. Low fat diet
C. Low selenium diet
D. Low protein diet

## Pancreatic Disorders

### Pancreatitis

202. All the following are causes of Acute Pancreatitis *except:* *(AI 1994)*
A. Gall stones
B. Alcohol
C. Hemochromatosis
D. Hypercalcemia

203. Increased amylase may be seen in all of the following *except* : *(AI 1997)*
A. Pancreatic pseudocyst
B. Appendicitis
C. Perforated peptic ulcer
D. Ruptured ectopic pregnancy

204. Raised serum amylase levels are used to diagnose
A. Autoimmune disease *(AIIMS May 04)*
B. Degenerative diseases
C. Acute cholecystitis
D. Acute pancreatitis

205. Ranson's critaria for prognosis in acute pancreatitis include all *except* : *(AI 1998)*
A. WBC>16,000 cells/cumm
B. Age over 55 years
C. AST > 250 U/100 ml
D. S. amylase > 350 I.U.

206. Which of the following is not a prognostic factor for Acute Pancreatitis *(AIIMS Nov. 06)*
A. Serum Amylase
B. Serum Calcium
C. Serum Glucose
D. Serum AST

207. Which one is not the bad prognostic sign for pancreatitis: *(AIIMS June 2000)*
A. TLC > 16000
B. Calcium less than 8 mmom/L
C. Glucose > 200mg%
D. Prothrombin > 2 times the control

208. Which one is not poor prognostic factor for acute pancreatitis: *(AIIMS Nov 99)*
A. Hyperglycemia
B. Hypocalcemia
C. Raised LDH level in blood
D. Hyperamylasemia

209. Monu, a 30 year old male, a chronic alcoholic presents with sudden onset of epigastric pain that radiates to the back. All are seen Except:
A. Low serum lipase *(AIIMS June 01)*
B. Increased LDH
C. Hypocalcemia
D. Increased serum amylase

210. Definitive laboratory diagnosis of acute pancreatitis is done by: *(AI 1993)*
A. Serum Amylase
B. Serum Lipase
C. Hyperglycemia
D. Hypercalcemia

211. The most specific laboratory test to establish a diagnosis of acute pancreatitis is: *(PGI 08)*
A. Serum amylase
B. Serum lipase
C. Serum Alkaline phosphatase
D. Serum Calcium
E. Serum glucose

212. Cause of acute loss of vision in a patient of alcoholic pancreatitis is: *(AI 95)*
   A. Purtscher's retinopathy
   B. Sudden alcohol withdrawal
   C. Acute congestive glaucoma
   D. CRAO
213. Cause of acute loss of vision in a patient of alcoholic pancreatitis is: *(AI 1995, 2000)*
   A. Purtscher's retinopathy *(AIIMS-99)*
   B. Sudden alcohol withdrawal
   C. Acute congestive glaucoma
   D. CRAO
214. Which of the following types of pancreatitis has the best prognosis? *(AI 2004)*
   A. Alcoholic pancreatitis
   B. Gall stone pancreatitis
   C. Post operative pancreatitis
   D. Idiopathic pancreatitis
215. Medical treatment of pancreatitis includes :
   A. Cholestyramine *(AIIMS May 94)*
   B. Aprotinin
   C. Calcium
   D. Glucagon
216. Most common complication of acute pancreatitis is:
   A. Pancreatic abscess *(AIIMS May 95)*
   B. Pseudocyst
   C. Phlegmon
   D. Pleural effusion
217. Pancreatic pseudocyst most commonly occurs after
   A. Trauma *(AI 1994)*
   B. Pancreatitis
   C. Pancreatic surgery
   D. Pancreatic malignancy
218. All are ture about pseudopancreatic cyst of pancreas *except* : *(AI 1998)*
   A. Common after acute pancreatitis
   B. Presents as an abdominal mass
   C. Serum amylase is increased
   D. Most common site is in head of pancreas
219. All of the following statements about Pseudopancreatic cysts are true *except* : *(AI 1997)*
   A. Percutaneous aspiration is treatment of choice
   B. Cystojejunostomy is treatment of choice
   C. Serum amylase levels are increased
   D. Presents as an epigastric mass

## Endocrinal Tumors of Pancreas

220. Which of the following is NOT secreted in pancreatic tumour : *(AIIMS Sep 96)*
   A. VIP
   B. Insulin
   C. Somatostatin
   D. ACTH
221. Zollinger-Ellison syndrome is characterized by all of the following *except* *(AI 1994)*
   A. Post bulbar ulcer
   B. Recurrent duodenal ulcer
   C. Severe diarrhea
   D. Massive HCL in response to histamine injection
222. The triad originally described by Zollinger Ellison syndrome is characterized by: *(AI 2002)*
   A. Peptic ulceration, gastric hypersecretion, non beta cell tumour
   B. Peptic ulceration, gastric hypersecretion, beta cell tumour
   C. Peptic ulceration, achlorhydria, non beta cell tumour
   D. Peptic ulceration, achlorhydria, beta cell tumour
223. All are true regarding Zollinger Ellison syndrome, *except:* *(AIIMS Dec 97)*
   A. Diarrhoea
   B. Recurrence after operation
   C. Hypergastrinemia
   D. Decreased ratio of BAO to MAO
224. Zollinger Ellison syndrome is characterized by high levels of: *(NBE)*
   A. Insulin
   B. VIP
   C. Gastrin
   D. Glucagon
225. Most important investigation for diagnosis of Zollinger Ellison-syndrome is : *(AI 1999)*
   A. $Ca^{++}$ infusion test
   B. Secretin injection test
   C. ACTH stimulation test
   D. Steroid assay
226. Best provocative test for diagnosis of Gastrinoma is: *(NBE)*
   A. $Ca^{++}$ infusion test
   B. Secretin injection test
   C. ACTH stimulation test
   D. Steroid assay
227. Drug of choice in Zollinger Ellison syndrome is
   A. Ranitidine *(AIIMS May 95)*
   B. Omeprazole
   C. Antacids
   D. B-blocker
228. Treatment of choice for ZES :
   A. PPI *(AI 2007)*
   B. Somatostatin analogues
   C. Streptozocin
   D. Sucralfate
229. Gold standard test for diagnosis of Insulinoma is :
   A. '72 hour' fast test *(AI 2009)*
   B. Plasma Glucose levels < 3 mmol/l
   C. Plasma Insulin levels > 6μU/ml
   D. C- peptide levels < 50 p mol/e
230. All of the following statements about Insulinoma are true Except: *(AI/AIIMS)*
   A. Most commonly found in 'Pancreas'
   B. Usually Benign

C. Usually multiple
D. Derived from Beta cells

231. Which of the following statements about Insulinoma is true: *(AIIMS)*
A. Present in Pancreas
B. Mostly malignant
C. Surgery is usually not required
D. Usually multiple

232. Weight loss may be seen in all of the following ***except*** : *(AI 1998)*
A. Uremia
B. Pheochromacytoma
C. Adrenal insufficiency
D. Insulinoma

233. All of the following about Gastrointestinal Carcinoid tumors are true, Except: *(AI 2010)*
A. Small intestine and appendix account for almost 60% of all gastrointestinal carcinoid.
B. Rectum is spared
C. 5 year survival for carcinoid tumors is >60%
D. Appendicial carcinoids are more commin in females than males.

234. The most classical symptom of VIPOMA is: *(NBE)*
A. Gall stones
B. Secretory diarrhea
C. Steatorrhea
D. Flushing

235. Pancreatic cholera is characterized by ***all except:***
A. Hypochlorhydria *(AI 1996)*
B. Hypokalemia
C. Glucose intolerance
D. Hypocalcemia

236. Which of the following statements about Pancreatic Carcinoma is not true : *(AI 2009)*
A. Mutation in $P^{53}$ gene is associated in 75% of cases
B. Hereditary Pancreatitis significantly increases the risk
C. Median survival in locally advanced (stage III) disease is 3- 6 months
D. Five year survival after curative pancreaticoduodenectomy is 15 – 20%

## Cystic Fibrosis

237. Which of the following statements about Cystic fibrosis (CF) is not true: *(AI 2009)*
A. Autosomal Recessive Disorder
B. Abnormality in CFTR which leads to defective Calcium Transport
C. Predisposition to pulmonary infection with Pseudomonas
D. Cirrhosis is an established complication of CF

238. A seven year old child with recurrent chest infections and exocrine pancreatic insufficiency is suspected of having cystic fibrosis Sweat chloride levels have been observed between 40-60 mmol/l on two separate occasions. Which of the following test should be performed next to support the diagnosis of Cystic fibrosis: *(AI 2009)*
A. Repeat Sweat chloride levels on a different day
B. Demonstrate an abnormal nasal potential difference
C. Demonstrate an abnormal F508 mutation by DNA analysis
D. Demonstrate an abnormal 72 hour fecal fat collection

## Miscellaneous

239. FOR the diagnosis of which of the following is the Alverado score used? *(NBE)*
A. Pancreatitis
B. Cholecystitis
C. Ulcerative colitis
D. Acute appendicitis

240. In the treatment of which of the following is the oschner sherren regimen used? *(NBE)*
A. Diverticulitis
B. Apendicular lump
C. Ilececal tuberculosis
D. Acute intestinal obstruction

241. Non invasive diarrhea is caused by: *(AI 2009)*
A. Shigella
B. B. Cereus
C. Salmonella
D. Y. enterocolitica

242. Features of secretory diarrhea include all of the following, Except: *(AI 2009)*
A. Stool volume > 1L /day
B. Normal osmotic anion gap
C. Reduces with fasting
D. Painless

243. A patient on treatment with ketoconazole for a fungal disease develops Gastroesophageal Reflux Disease (GERD). Which of the following drugs should not be prescibed to him: *(AI 2012)*
A. Cisapride
B. Itopride
C. Metoclopramide
D. Domperidone

244. Which of the following is the commonest cause of lower GI bleed: *(PGI Dec 04)*
A. Angiodysplasia
B. Enteric fever
C. Diverticulosis
D. Colonic polyps
E. Hemorrhoids

245. An elderly patient presents with a prolonged history of weakness and lethargy. On examination he is found to be anemic and stool is positive for occult

blood. Which of the following is the investigation of choice: *(AI 2010)*
A. Colonoscopy
B. Barium meal
C. Barium enema
D. CT abdomen

246. Massive bleeding per rectum in a 70 yr old patient is due to : *(AI 2000)*
A. Diverticulosis
B. Carcinoma colon
C. Colitis
D. Polyps

247. A man aged 60 yrs has h/o IHD and atherosclerosis. He presents with abdominal pain and maroon stools: likely diagnosis here is: *(AI 2001)*
A. Acute intestinal obstruction
B. Acute mesenteric ischemia
C. Peritonitis
D. Appendicitis

248. Intestinal hypomotility is seen in all the following *except:* *(AI 1995)*
A. Diabetes
B. Parkinsonism
C. Amyloidosis
D. All of the above

249. Gastric motility decreases in A/E: *(NBE)*
A. Diabetes
B. Upper abdominal surgery
C. Stroke
D. Hyperthyroidism

250. Gastrointestinal Motility is decreased in all of the following, except: *(NBE)*
A. Amyloidosis
B. Diabetes
C. Scleroderma
D. Hyperthyroidism

251. The most common cause of seizures in children with diarrhea is: *(NBE)*
A. Hypokalemia
B. Hyperkalemia
C. Hyponatremia
D. Hypernatremia

252. All of the following statements stand true for telengiectasia of colon *except* : *(AI 1998)*
A. May be seen in person less than 40 years of age
B. May be seen in person more than 60 years of age
C. Common site is caecum
D. 50% involve rectum

253. Hypergastrinemia with hypochlorhydria is seen in:
A. Zollinger Ellison Syndrome *(AI 2002)*
B. VIPoma
C. Pernicious anemia
D. Glucagonoma

254. Hypergastrinemia with hypochlorhydria is seen in:
A. Zollinger Ellison Syndrome *(AI 2002)*
B. VIPoma
C. Pernicious anemia
D. Glucagonoma

255. A young patient presenting with massive hematemesis was found to have splenomegaly. In this case the most likely source of bleeding is: *(AI)*
A. Duodenal ulcer
B. Esophageal varices
C. Erosive mucosal disease
D. Gastric ulcer

256. All of the following statements about Mucosa Associated Lymphoid Tissue Lymphomas (MALT) are true, Except: *(PGI June 05)*
A. Present at extranodal sites
B. Predisposed by H. Pylori infection
C. Present as stromal polyps
D. Are sensitive to chemotherapy

257. The advantage of Bladder drainage over Enteric drainage after Pancreatic Transplantation is better monitoring of : *(AI 2009)*
A. HBA1C levels
B. Amylase levels
C. Glucose levels
D. Electrolyte levels

258. Parastomal hernia is most frequently seen with:
A. End Colostomy *(AI 2009)*
B. Loop Colostomy
C. End Iliostomy
D. Loop Iliostomy

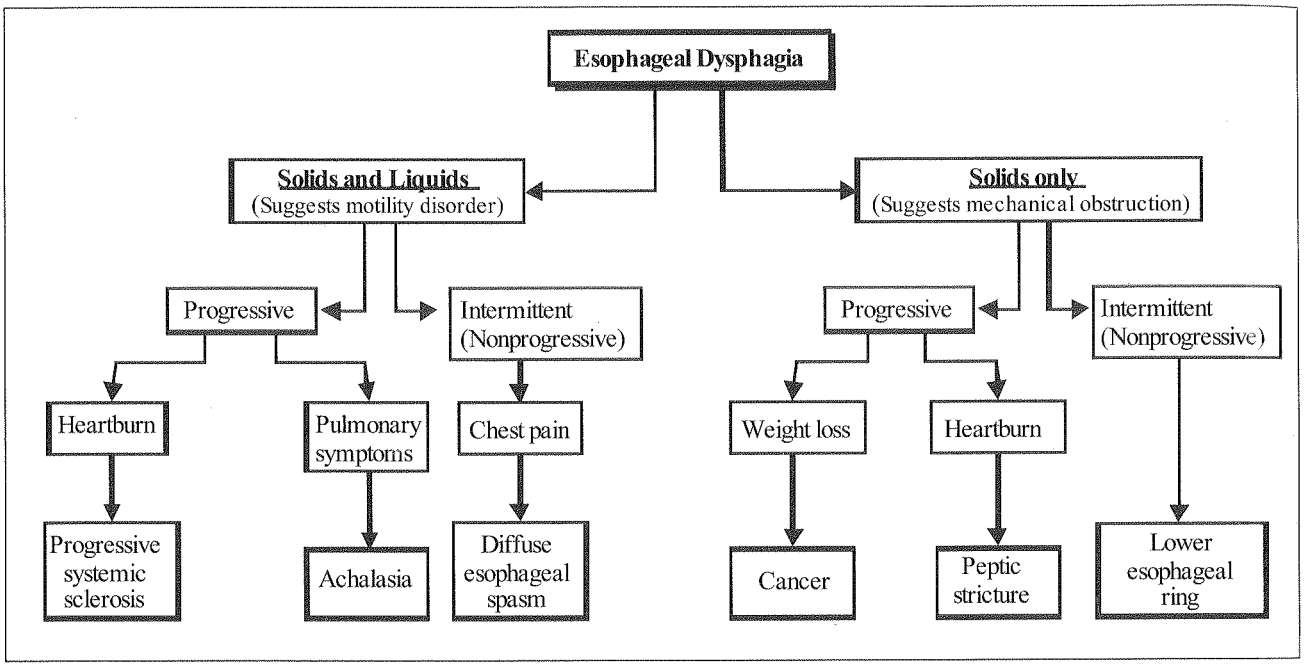
## ANSWERS, REFERENCES, EXPLANATIONS AND RELEVANT HIGH YIELD FACTS

### Esophageal Conditions

### Dysphagia (General / Differential Diagnosis):

1. **Answer is B (Multiple sacculations and pseudodiverticulae Corkscrew esophagus):** *Current Diagnosis and Treatment in Gastroenterology 2nd/288; Harrisons 16th/1742*

***The presence of non progressive dysphagia to both solids and liquids suggests the diagnosis of diffuse esophageal spasm. The charachteristic barium swallow findings in diffuse esophageal spasm is the corkscrew esophagus (appearance of curling or multiple ripples in the wall, sacculations and pseudodiverticula)***




- Rat tail esophagus with a dilated proximal esophagus and narrow lower end suggests a diagnosis of Achlasia cardia. *(Dhingra 4th/305)*

  Achlasia is associated with *Progressive dysphagia* to *both solids and liquids*
- Narrow and irregular esophageal lumen suggests a diagnosis of esophageal carcinoma *(Dhingra 4th/306)*

  Esophageal carcinomas are associated with *progressive dysphagia*. Which is *initially only for solids* at presentation (may prgress to cause dysphagia to liquids also)
- Stricture or ulcer in the esophagus suggests a diagnosis of Gastrophageal Reflux disease (GERD) *(H16th/1743)*
  GERD is asociated with *progressive dysphagia* to *solids alone* at presentation.

2. **Answer is D (Lower esophageal ring) :** *Current Diagnosis and Treatment in Gastroenterology 2nd/288; Harrison's 17th/239, 240, 1854*

***Non progressive (episodic) dysphagia only for solids is characteristic of lower esophageal rings (Schatzki's ring). The ring is apparent as a constriction in the lower esophagus on barium swallow.***

*Peptic stricture and carcinoma esophagus present with **progressive** dysphagia for solids while Achalasia presents with **progressive** dysphagia for both solids and liquids.*

3. **Answer is C (Achalasia Cardia):** *Refer previous question*

*Carcinoma Esophagus, lower esophagus ring and esophageal stricture are all associated with dysphagia for solids alone.*

***Presence of dysphagia for both solids and liquids suggests a diagnosis of Achalasia cardia.***

*Although dysphagia in Achalasia is progressive absence of progression does not exclude the diagnosis. Also amongst the options provided Achalasia is the single best answer of exclusion.*

4. **Answer is C and D (Pharyngeal diverticulum) and (Diffuse esophageal spasm):** *Current Gastroenterology 2nd/288; Harrisons 16th/217; CMDT 2005/546; 09/514*

| Progressive | Intermittent |
|---|---|
| • *Achalasia*<br>• *Progressive systemic sclerosis*<br>• *Peptic stricture*<br>• *Carcinoma* | • *Lower esophageal ring/Spatzki ring*<br>• *Diffuse esophageal spasm*<br>• *Zenker's diverticulum* |

5. **Answer is B (Endoscopy):** *CMDT 09/514; Refer text below*

***Dysphagia for solids alone suggests a probable mechanical cause for dysphagia such as carcinoma, stricture or esophageal web. The investigation of choice for such cases is Endoscopy.***

Esophageal Dysphagia

*Initial investigation should be Barium swallow*

| Dysphagia for both liquids & solids | Dysphagia for solids alone |
|---|---|
| Suggests esophageal motility disorder<br>- *Achalasia*<br>- *Diffuse Esophageal spasm* | Suggests mechanical obstruction<br>- *Carcinoma*<br>- *Stricture*<br>- *Web* |
| ↓ | ↓ |
| ***Investigation of choice is Manometry*** | ***Investigation of choice is endoscopy*** |

6. **Answer is D (Manometry):** *Mayo Clinic Gastroenterology and Hepatology Board Review 4th/ 31, 32*

*Esophageal manometry is the gold standard test for esophageal motility disorders.*

| Esophageal Motility Disorders : Manometry is the test of choice |
|---|
| Achalasia Cardia |
| Diffuse Oesophageal Spasm (Discoordinated motility) |
| Nutcracker Oesophagus (Hypercontractile motility) |
| Hypertensive LES (Hypercontractile motility) |
| Hypotensive LES(Hypocontractile motility) |
| Ineffective Oesophageal motility (Hypocontractile motility) |

7. **Answer is B (Upper GI endoscopy is to be done):** *Refer previous question*

***The patient is presenting with new onset dysphagia for solids alone (able to swallow liquids). This suggests dysphagia due to mechanical obstruction (carcinoma, stricture, web) which is best diagnosed by endoscopy.***

Note:
*Barium swallow is the recommended initial investigation*
*Endoscopy is the investigation of choice.*

**8. Answer is D (Compression by an aberrant blood vessel):** *Bailey 24th/995; 23rd/859*

***Dysphagia Lusoria refers to dysphagia arising from symptomatic compression of the esophagus by an aberrant blood vessel.***

**9. Answer is C (Tertiary):** *Bailey Love 25th/ 1010, 1011, 'Board Review series (BRS): General Surgery' (2000)/ 240, Review of Surgery' by Mostafa (2006)/189*

***Simultaneous, Non progressive, Non Peristaltic waves are called Tertiary contractions.***

**Tertiary Contractions of Esophagus**

- Tertiary contractions are simultaneous, non progressive, non peristaltic waves that can occur throughout the esophagus
- Tertiary contractions represent uncoordinated contractions of the smooth muscles that are responsible for the 'Cork Screw' appearance of esophageal spasm on Barium swallow
- Tertiary contractions do not have a physiological function and may be observed in the elderly and in patients with esophageal motility disorders.

Three types of Contractions are seen in Esophagus

| Primary Contractions (Primary Peristalsis) | Secondary Contractions (Secondary Peristalsis) | Tertiary Contractions (Tertiary Peristalsis) |
|---|---|---|
| • *Progressive contractions* | • *Progressive contractions* | • ***Non progressive contractions*** |
| • Triggered by voluntary swallowing | • Triggered by distension or irritation of esophagus (but not by voluntary swallowing) | • Occur spontaneously and simultaneously between swallows |

## Achalasia Cardia

**10. Answer is A & B (Dysphagia is the presenting symptom) and (The cause is the absence of Auerbach's plexus):** *Current Diagnosis & Treatment in Otorhinolaryngology 2nd/ ; Harrison 18th/p 2430, 2431, 2432; 17th/1849, 1850*

***Dysphagia is the most common presenting symptom of Achalasia which is believed to be caused by degeneration of the Myenteric plexus of Auerbach***

Esophagectomy is not used in the treatment
The surgical treatment of Achalasia is Heller's myotomy and not ***Esophagectomy.***
**Medications** that relax the tone of Lower Esophageal Sphincter are used in the treatment.
**Barium swallow** shows a dilated sigmoid esophagus and persistent beak like narrowing of distal esophagus.
*Irregular filling defects in lower esophageal suggests esophageal carcinoma and not Achalasia.*

**Achalasia Cardia (Primary esophageal motility disorder)**

Physiological Characteristic

- Absence of esophageal peristalsis
- Increased pressure of LES
- Failure of LES to relax in response to swallowing

Pathogenesis

- True etiology unknown
- Degeneration of Myenteric plexus of Aurerbach's with loss of postganglionic inhibitory neurons is noted (These neurons contain NO and VIP which mediate LEs relaxation)
- Sparing of postganglionic cholinergic fibres
  (Increased Les resting pressure and insufficient relaxation)

Presentation

- Dysphagia is the most common symptom
  Dysphagia is present for both solids and liquids and is progressive
- Regurgitation is the second most common symptom
- Chest pain may also occur

Investigations

- *Esophageal Manometry is the key test in establishing the diagnosis*
- *Barium swallow should be the initial test performed*

Diagnosis suggested by:
- *Dilated sigmoid oesophagus*
- *Persistant beak like narrowing of distal oesophagus*

Complications

Achalasia is a risk factor for Esophageal carcinoma[Q]
Achalasia predisposes to squamous cell carcinoma[Q]

Treatment

*Laparoscopic Heller's myotomy[Q] and partial fundoplication is the procedure of choice*
Non surgical treatment includes medications that reduces LES pressure
- Intrasphinteric injection of botulinum toxin and/or
- Pneumatic dilatation

11. **Answer is A (Pressure at distal end increased with no peristalsis):** *Current Diagnosis & Treatment in Otorhinolaryngology 2nd/ ; Harrison 18th/p 2430, 2431 Harrison 17th/1849, 1850; Current Diagnosis & Treatment in Gastroenterology 2nd/287*

*Achalasia is characterized by an increased pressure of LES and absence of esophageal peristalsis.*

Physiological /Manometric features of Achalasia

- *Elevated Resting pressure of LES (>45 mmHg)[Q]*
- *Incomplete LES relaxation (in response to swallowing) [Q]*
- *Absence of distal esophageal peristalsis [Q]*

12. **Answer is A (Achlasia cardia) :** *Dhingra ENT 3rd/400*

*Presence of dysphagia which is more for liquids than for solids along with a characteristic rat tail appearance on radiography in a young patient suggests the diagnosis of achalasia.*

**Malignancy (CA esophagus)** usually presents with dysphagia which is more for solids than for liquids and is seen in the elderly.

**Zenker's diverticulum and esophageal spasm** do not show a rat tail appearance on radiography.

13. **Answer is A (Barium swallow):** *Current Diagnosis & Treatment in Otorhinolaryngology 2nd/488*

*Presence of progressive dysphagia for both liquids and solids suggest a probable diagnosis of Achalasia Cardia. Barium swallow should be the first / initial investigation.*
*'In evaluating a patient with dysphagia, a barium swallow should be the first test performed'-Current Otorhinology 2nd/488*

14. **Answer is A (Achalasia Cardia):** *Harrison 18th/p 2432 Harrison 17th/1850*

*Heller's extramural myotomy of the LES is performed for Achalasia cardia and involves incising the circular muscle layer.*

15. **Answer is A (Achalasia Cardia)**

*Heller's cardiomyotomy is the standard surgical treatment for Achalasia Cardia.*

The first successful surgery for Achalasia Cardia was performed in 1913, by the German surgeon Ernest Heller

## Diffuse Esophageal Spasm

16. **Answer is B (Manometry) :** *Bailey 25th/ 1039, CSDT 12th/458, Sabiston 18th/1069*

*Diffuse oesophageal spasm is a type of oesophageal motility disorder. Such Motility disorders are best diagnosed by Manometry studies*

*'Esophageal manometry is the key test for establishing the diagnosis of diffuse esophageal spasm' – CSDT*
*'Esophageal manometry is the only test that distinguishes diffuse esophageal spasm from other primary esophageal motor disorders – CSDT/458*

**Diffuse Esophageal spasm:**

Diffuse Esophageal spasm is a poorly understood hypermotility disorder of the oesophagus

**Presentation**

- The clinical presentation is typically that of *Chest pain and Dysphagia*
- ***'The most common symptom is intermittent chest pain***$^{Q}$ ( >dysphagia)
- Chest pain mimics angina or pain of coronary artery disease
  - *Squeezing pressure in the chest that may radiate to the Jaw, arms or upper back*
  - *Symptoms are aggravated by emotional stress, exertion (or related to eating)*

*Chest pain*$^{Q}$
*Dysphagia*$^{Q}$

**Diagnosis**

***Manometry is the key to establish the diagnosis***
*The diagnosis is usually made by an esophagogram (Barium swallow) and monometric study*
*Ambulatory pH monitoring should be performed to rule out abnormal reflux*

Esophagogram (Barium Swallow)

- *Corkscrew esophagus*$^{Q}$ is *classical of Diffuse esophageal* spasm (seen in about 30% of cases)

(Radiological evidence of tertiary contractions)

| Ambulatory 24 hour pH monitoring |
|---|
| *Gastro esophageal reflux disease may mimic diffuse esophageals spasm Ambulatory pH monitoring must be performed to rule out abnormal reflux which is the most common cause of non cardiac chest pain* |

Manometry

- ***Manometry is the key to establish the diagnosis (CSDT)*** *Correlation of subjective complains with evidence of spasm (induced by vagomimetic drug bethenechol) on manometric studies prvide convincing evidence*-Sabiston
- *Esophageal monometry is the only test that distinguishes diffuse esophageal spasm from other primary esophageal motor disorders* - CSDT
- *An ambulatory motility record (ambulatory manometry) is preferred over standard manometry* as contractions are intermittent and normal peristalsis is seen in between. *Ambulatory manometry is the single best investigation with a sensitivity of 90% and specificity of 100%*

**17. Answer is D (Diffuse Esophageal Spasm) :** *Harrison 15th/1645; Dhingra 3rd/399; Bailey 22nd/660; 24th/1020*

***Diffuse esophageal spasm is synonymous with 'corkscrew esophagus' or Rosary esophagus - Bailey***
*In diffuse esophageal spasm, barium swallow shows that normal sequential peristalsis below the aortic arch is replaced by uncoordinated simultaneous contractions that produce the appearance of curling or multiple ripples in the wall, sacculations, and pseudodiverticula- the "corkscrew" esophagus.*

**18. Answer is D (Diffuse Esophageal Spasm):** *Repeat*

***Corkscrew Esophagus is synonymous with Diffuse Esophageal Spasm.***

**19. Answer is D (Diffuse Esophageal Spasm):** *Repeat*

***Corkscrew Esophagus is synonymous with Diffuse Esophageal Spasm.***

## Zenker's Diverticulum

**20. Answer is A (Zenker's diverticulum)** : *Dhingra 3rd/330*

***Regurgitation of food eaten 3 days ago hints to the possibility of another sac / diverticulum which stores food. Age of the patient and gurgling sound support the diagnosis of Zenkers diverticulum.***

**Zenker's diverticulum**

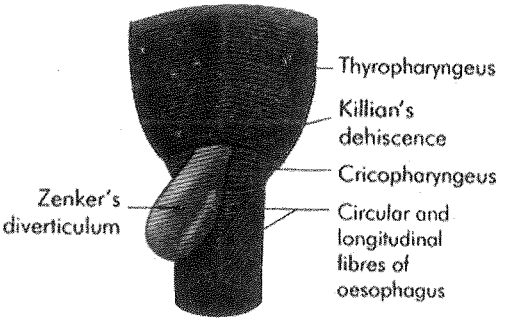
| What it is : |
|---|
| It is a *pulsion diverticulum*[Q], where pharyngeal *mucosa*[Q] herniates *through the Killihan's dehiscence*[Q] (a weak area *between two parts of Inferior Constrictor*[Q]). |
| **Age of presentation** |
| This condition is usually seen after 60 years of age (*elderly*) [Q] |
| **Symptomatology / presentation** |
| • ***Dysphagia***[Q] : As mouth of the sac is wider than the opening of esophagus, food preferentially enter the sac. When the pouch gets filled with food, it presses on the esophagus & produces ***Dysphagia***. [Q]<br>• ***Gurgling Sound***[Q] is produced during swallowing.<br>• Halitosis or foul smell is frequently associated<br>• ***Cough & Aspiration pneumonia***[Q] : food eaten *over the last few days*[Q] may regurgitate as it collects in the pouch causing cough and aspiration pneumonia.<br>• ***Malnutrition***[Q] : Patient is often malnourished due to dysphagia. |

21. **Answer is D (Out pouching of the anterior pharyngeal wall, just above the cricopharyngeus muscle.)** *Current Diagnosis & Treatment in Otorhinology 2nd /490, Dhingra 4th/355; Fem's Colour Atlas and Text of Clinical Medicine (2008)/560, 'Clinical scenarios in Thoracic Surgery' by Kalimi (2004) / 254*

***Zenker's diverticulum is an out pouching of the posterior pharyngeal wall where pharyngeal mucosa herniates through the Killians dehiscence (a weak area between cricopharyngeus inferiorly and thyropharyngeus superiorly both being parts of the inferior constrictor).***

**Zenker's diverticulum originate from the posterior wall of pharynx and not from the anterior wall**

- Zenker's diverticulum originates from the *posterior wall* of the pharynx through the killian's dehiscence
- Killian's dehiscence is a weak area between
  - Oblique fibres of the Thyropharyngeus (part of inferior constrictor muscle) superiorly
  - Transverse fibres of the cricopharyngeus (part of the inferior constrictor muscle) inferiorly
- Herniation *starts in the midline posteriorly*, however as the out pouching enlarges, it localizes to one side of the oesophagus most commonly on the left side.




Hypopharyngeal (Zenker's) diverticulum.
Hypopharyngeal mucosa herniates through the Killian's dehiscence a weak area between two parts of inferior constrictor

**Zenker's diverticulum is an acquired diverticulum and not a congenital diverticulum**

Zenker's diverticulum is a *believed to be an acquired disorder* that results when mucosal and submucosal layers herniates through the killian's dehescence, a weak area between two parts of the inferior constrictor.

These are *acquired pulsion diverticulae* that usually occur in people older than 60 years as their pharyngeal muscle tone and elasticity decreases.

**Zenker's diverticulae are false diverticulae**

Zenker's diverticulum *is a false diverticulum* because it does not contain all the anatomic layers of the esophageal wall Zenker's diverticulum involves protrusion of *only the mucosa (and submucosa)* through the posterior muscle layers

**Zenker's diverticulum are often identified by Lateral x-rays on Barium swallow**

Barium swallow is the diagnostic procedure of choice for Zenker's diverticulum

*'The diagnosis is most easily made with a lateral view of cervical esophagus during barium esophagography'*
*- 'Gastroenterological Endoscopy' by Classes (2002) / 474*

*'Lateral x- Rays on barium swallow are essential because these are posterior out pouchings'*
*- 'Review of surgery' by Mostafa (2006) / 197*

**22. Answer is A (Zenker's diverticulum):** *Refer previous question; Current Otolaryngology 2nd/490*

***Presence of intermittent dysphagia for solids, regurgitation of food and halitosis (foul smell) suggests a diagnosis of Zenker's Diverticulum.***

Essentials of Diagnosis : Zenker's Diverticulum (Current Otolaryngology)

- *Dysphagia (Intermittent)*
- *Regurgitation of undigested food (with risk of aspiration)*
- *Gurgling sounds in neck*
- *Halitosis*

**23. Answer is C (Lung Abscess):** *Refer text below*

***The most frequent complications of Zenker diverticulum is 'aspiration' into the tracheobronchial tree which can in turn present with pneumonia and Lung Abscess.***

**24. Answer is C (Treatment is Simple excision) :** *Dhingra 2nd / 271*

***Zenker's diverticulum may be managed by simple excision of the pouch.***

**Zenker's diverticulum is usually symptomatic and not asymptomatic**

**Characteristic symptoms of Zenker's Diverticulum**

***Intermittent dysphagia***
***Regurgitation***
***Gurgling sound in neck***
***Halitosis***

**Zenker's Diverticulum occurs in the pharynx and not in the esophagus**

***Zenker's diverticulum*** or ***'Hypopharyngeal Diverticulum'*** is a '*Pulsion diverticulum*' where pharyngeal mucosa herniates through the Killan's dehiscence Q. (*Killan's dehiscence*Q is a weak area of pharynx between two parts of inferior constrictor muscleQ)

- Usually seen ***in elderly (after 60 years of age)***Q
- Herniation starts in midline and lies first behind the esophagus and then to its left. ***(it occurs in pharynx and not in esophagus)***. Mouth of the sac is wider than the opening of esophagus and food preferentially enters the pouch.

  - ***Dysphagia is the prominent manifestation.*** It appears after a few swallows.
  - When pouch gets filled with food, it presses on the esophagus.
  - Gurgling sound is produced on swallowingQ
  - Food may regurgitate at night when patient is recumbent causing cough and aspiration pneumonia
  - Patient is malnourished due to dysphagia

Zenker's diverticulum is usually seen in elderly and not in children.
*Condition is usually sen after 60 years of age (elderly)*
***Zenker's diverticulum may be managed by simple excision of the pouch***

**Treatment options for Zenker's diverticulum**

- Simple Excision of pouch
- ***Excision of pouch and cricopharyngeal myotomy*** Q
- ***Dahlman's procedure***Q :Done in poor-risk debilitated patients. The partition wall between esophagus and pouch is divided by diathermy.

## Oesophageal Ring / Web

**25. Answer is A & C (Mucosal ring at squamo-columnar junction) & (Dysphagia is the presenting symptom):** *Oxford textbook of Medicine 4th/553*

*Schatzki ring is a mucosal / submucosal ring at the squamo-columnar junction of distal esophagus that may present with intermittent dysphagia.*

**Schatzki Ring (Oesophageal Ring)**

- *It is a characteristic short segment of luminal stenosis*
- ***Occurs in the lower esophageal at the gastroesophageal junction (squamo-columnar junction)***
- ***It is made up only of mucosa and submucosa and narrows the lumen only to a few millimeters.***
- *True aetiopathogenesis is not known*
- *Usually asymptomatic*
- ***Most common presentation intermittent dysphagia only for solids.***
- *Often associated with a hiatus hernia.*
- *Frequently leads to incorrect diagnosis of diffuse esophageal spasm*
- *Treatment involves esophageal dilatation or endoscopic diathermy/laser.*

**26. Answer is D (Common in elderly male):** *Harrison 14th/1595; Harrison 15th/1648, 579; (Not in Harrison 16th) Kumar Clark 5th/267; Dhingra 3rd/399; Harrison 17th 1854 Harrison 18th/p 2429*

*'Plummer Vinson syndrome refers to the combination of hypopharyngeal webs and iron deficiency anemia in middle aged women' – Harrison*

**Plummer Vinson Syndrome (Patterson Kelly)**

- Upper esophageal web
- Iron deficiency anemia
- Koilonychia
- Glossitis and angular stomatitis

## Barret's Esophagus

**27. Answer is B (Intestinal Metaplasia):** *Harrison 18th/p2434 Harrison 17th/1852; Current Diagnosis & Treatment in Gastroenterology/227*

*Barret's esophagus is a metaplasia of the esophageal mucosa caused by replacement of squamous epithelium with columnar epithelium.*
*Specialized intestinal epithelium (intestinal metaplasia) is the most common and most important type of columnar epithelium seen in Barret's esophagus.*

**Barret's esophagus (columnar metaplasia)**

**Metaplasia of squamous epithelium into columnar epithelium**

↓

**Three types of Columnar Epithelium may be seen**

**Gastric Type**
*Morphologically indistinguishable from normal gastric epethelia*

**Junctional Type**
*Morphologically indistinguishable from normal gastric epethelia*

**Intestinal Type**
*Morphologically distinct and readily distinguishable from gastric epethelia*
- This is the most common type
- Most commonly associated with dysplasia & carcinoma

**28. Answer is A (More incidence of squamous carcinoma):** *Harrison 18th/p2434 Harrison 17th/1852*

*Barret's oesophagia is associated with an increased incidence of adenocarcinoma and not squamous cell carcinoma.*

*Barret's esophagus is associated with columnar metaplasia of distal (lower esophagus).*

**29. Answer is A & C (Stricture and Peptic ulcer):** *Manual of Gastroenterology 4th/132*

*Complications of Barret's esophageal includes peptic ulceration, strictures and adenocarcinoma.*

Complications of Barret's Oesophagus

- *Peptic Ulcer (Barret's Ulcer: Chronic Peptic Ulceration in the columnar lined mucosa)*
- *Strictures*
- *Adenocarcinoma (Dysplagia – cancer sequence)*

**30. Answer is a D (Associated with oesophageal varices):** *Harrison 18th/p 2434 Harrison 17th/1852*

*Barret's oesophagus is not associated with oesophageal varices.*

*Barret's oesophagus is characterized replacement of lower oesophageal mucosa by intestinal (columnar) type of epithelium. It is considered premalignant with increased risk of adenocarcinoma, and is believed to be caused by prolonged gastroesophageal reflux.*

**31. Answer is E (None):** *Harrison 18th/p 2434 Harrison 17th/ ; Current Diagnosis and Treatment in Gastroenterology 2nd/277; Current Diagnosis and Treatment in Otorhinology 2nd/496*

*All statements about Barret's Esophagus are true*

- **Stricture in Barret's esophagus may present in high oesophagus**
  *Barret's oesophagus can also lead to chronic peptic ulcers of the esophagus with high and long strictures*
  *—Harrison 17th/1852*
- **Barret's esophagus is premalignant**
  *Barret's esophagus can progress to adenocarcinoma*
- **Diagnosis can be suggested by Endoscopy**
  *Endoscopy shows a 'salmon pink' epithelium above the gastroesophageal junction which replaces the whitish squamous epithelium.*
- **Diagnosis is confirmed by biopsy**
  *Diagnosis is confirmed by pathological examination and requires the identification of columnar (intestinal) type epithelium characterized by the presence of goblet cells.*

Barret's Esophagus

- *Metaplasia of esophageal squamous epithelium into columnar in distal oesophagus* Q
- *Most common type of columnar epithelium is intestinal epithelium (intestinal metaplasia)* Q
- *Metaplasia characteristically affects the distal (lower) oesophagus* Q
- *It is consequence of severe reflex esophagitis* Q
- *More common in men* Q *(Males > Females)*
- *More common in whites* Q *(Whites > Blacks)*
- *More common with increasing age* Q *(incidence increases with age)*
- *Considered a premalignant condition* Q
- *Type of cancer associated in an adenocarcinoma* Q
- *Columnar metaplasia that carries maximum risk of adenocarcinoma is intestinal metaplasia (intestinal epithelium)* Q
- *Can lead to chronic peptic ulceration of esophagus* Q *(Barret ulcer)*
- *Can lead to high (midoesophageal) and long strictures* Q

**32. Answer is B (Premalignant condition):** *Harrison 18th/p 2434 Harrison 17th/1852, 1853*

*Barret's oesophagus is a premalignant condition with increased risk of adenocarcinoma.*

**Barret's esophagus is more common in males**
*More common in males (Males > Females)*[Q]
*More common in White (Whites > Blacks)*[Q]
*More common with increasing age*[Q]
**Barret's metaplasia once established does not respond to conservative management**

'Established Metaplasia does not regress with antisecretory treatment' – Harrison

*Although medical treatment does not regress the metaplastic changes, it is still advocated to prevent continued insult.*

**Barret's esophagus is associated with columnar metaplasia and not squamous metaplasia.**

33. **Answer is A (Adenocarcinoma):** *Harrison 16th/1852; CMDT 2008/562; 09/516*

***Barret's esophagus is a premalignant lesion and predisposes to adenocarcinoma of the lower (distal) esophagus.***

## Mallory Weiss Syndrome

34. **Answer is D (Mucosal tear):** *Harrison 18th/p 2436, 320 Harrison 17th -1854, 257*

***Mallory-Weiss Syndrome is associated with a tear of the gastric mucosa near the squamocolumnar mucosal junction***

| Mucosal Tear (Mallory-Weiss Syndrome) |
|---|
| • The tear usually involves the gastric mucosa near the squamocolumnar mucosal junction near cardia |
| • This tear is usually caused by vomiting, retching, or vigorous coughing. |
| • The tear is usually linear. |
| • Patients present with upper gastrointestinal bleeding ***(Hemetemesis)*** |
| • Association with alcoholism and hiatus hernia |
| • In most patients, bleeding ceases spontaneously<br>(Continued bleeding may respond to vasopressin therapy or angiographic embolization. Surgery is rarely needed) |

## Esophageal Carcinoma

35. **Answer is A (Squamous cell ca):** *Current Diagnosis and Treatment in Gastroenterology/299; CSDT/469*

*'By far the most common esophageal cancer world wide is squamous cell carcinoma' – Current Gastroenterology*

*'Over the past few decades there has been a progressive increase in the incidence of adenocarcinoma of the distal esophagus so that it accounts for more than 50% of all new cases of esophageal cancer.* ***Squamous cell carcinoma is still the most common type world wide'*** *– CSDT/469*

Confusing inference
*Most prevalent esophageal cancer world wide (old + new cases) is Squamous cell ca*
*Most common esophageal cancer world wide (new cases) is Adenocarcinoma*

36. **Answer is C (Lower 1/3rd):** *Harrison 16th/524*

***The lower third of the esophagus is the most common site of esophageal cancer and accounts for about 50% of all esophageal cancers.***

'*About 15% of esophageal cancers occur in the upper third of esophagus (cervical esophagus), 35% in the middle third of esophagus and 50% in the lower third'* – Harrison 16th/524

| Site of esophageal cancer (All histological types) | % of total |
|---|---|
| Upper 1/3rd | 15% |
| Middle 1/3rd | 35% |
| ***Lower 1/3rd*** | ***50%*** |

Note:
***The most common site of squamous cell (histological subtype) is middle 1/3 of esophagus*** Q
***The most common site of adenocarcinoma (histological subtype) is lower 1/3rd of esophagus*** Q.

**37. Answer is B (Middle 1/3rd):** *Sabiston 17th/1119; Devita 7th/866; Robbins 7th/807*

***The most common site of squamous cell carcinoma of esophagus is middle 1/3rd.***

| Site of squamous cell carcinoma | Percentage of total |
|---|---|
| Upper 1/3rd | 20% |
| ***Middle 1/3rd*** | ***50%*** |
| Lower 1/3rd | 30% |

**38. Answer is C (Lower 1/3rd):** *Refer text below*

***The most common site of adenocarcinoma esophagus is the lower 1/3rd of esophagus***

*Esophageal Adenocarcinoma invariably arises from Barret's esophagus (Barret's ulcer) which is characteristically located in the distal esophagus around the gastroesophageal junction.*

**39. Answer is B (Middle 1/3rd):** *API 7th/1012*

***Eighty to ninety percent of esophageal cancers in India are squamous cell carcinomas, and the most common site is middle 1/3rd of esophagus.***

**Remember**

| | |
|---|---|
| *Most common site of esophageal carcinoma in India* | *: Middle 1/3rd* |
| *Most common site of esophageal carcinoma world wide* | *: Lower 1/3rd* |

**40. Answer is D (Benzene therapy) :** *Harrison 15th / 578; Harrison 16th/524; Harrison 17th/570, 571 Harrison 18th/p 764*

***Benzene therapy has not been mentioned in the best of predisposing factors for carcinoma esophagus, and is the single best answer of exclusion.***

**Predisposing factors for carcinoma esophagus :**

| |
|---|
| 1. ***Alcohol consumption*** Q |
| 2. ***Smoking cigarettes*** Q |
| 3. **Ingested Carcinogens** |
| *Nitrates* Q<br>Smoked opiates<br>Fungal toxins in pickled vegetables |
| 4. **Mucosal damage** |
| ***Chronic Achalasia*** Q<br>Lye ingestion / Hot tea<br>Radiation induced strictures Q |
| 5. **Host Susceptibility** |
| 1. *Patterson Kelley syndrome* Q *or* ***Plummer Vinson syndrome*** Q<br>*Esophageal web* Q *+ Glossitis* Q *+ Iron deficiency* Q<br>2. ***Tylosis palmaris et plantaris*** Q *: Congenital hyperkeratosis* Q *and pitting of palms and soles* Q |
| 6. *Chronic Gastric Reflux, ie. Barrett's esophagus for Adenocarcinoma* Q |

**41. Answer is D (Ca Esophagus) :** *Harrison 15th/579; Harrison 16th/524; Harrison 17th/570, 571 Harrison 18th/p 764*

***Congenital hyperkeratosis and pitting of palms and soles (i.e tylosis palmaris et plantaris) is a known etiological factor for squamous Ca of Esophagus' – Harrison***

**42. Answer is B and D (Scleroderma and Barrets esophagus):** *Current Gastroenterology/300; Harrison 17th/570 Harrison 18th/p 764*

*Barret's esophagus is the characteristic risk factor for adenocarcinoma esophagus.*
*Scleroderma also increases the risk of esophageal adenocarcinoma perhaps through the development of Barret's esophagus as the collagen deposits in the distal esophagus cause LES dysfunction.*

**Risk factors for esophageal adenocarcinoma** *(Current Gastroenterology)*

- ***Barrets esophagus***
- *Gastroesophageal Reflux Disease (GERD)*
- ***Scleroderma***
- *Smoking*
- *Alcohol*
- *History of colon cancer*
- *Medications : Long term use (> 5 years) of Theophylline & β agonists.*

**43. Answer is A (Barrett's Esophagus) :** *Harrison 18th/p 764 Harrison 17th/571, 1852; Schwartz Pre-Test/Q.434*

*In barrett's esophagus there is a metaplastic change in the esophageal mucus membrane. The resulting columnar epithelium is susceptible to the development of the adenocarcinoma. The risk of developing adenocarcinoma in Barret's esophagus is 50-100 time, that of general population. If 100 patients with Barrett's esophagus are followed prospectively for one year, one adenocarcionom can be expected in that group.*
*Alcohol abuse, achalasia, lye stricture and smoking are all risk factors for the development of squamous carcinoma of the esophagus.*

**44. Answer is B (Barret's esophagus) :** *Harrison 17th/1852; Bailey Love 23rd/870*

*Adenocarcinoma is seen in Barret's esophagus*

**Barret's esophagus** is a metaplastic change in the lining mucosa of oesophagus in response to chronic gastroesophagus reflex.
In Barret's esophagus the junction between oesophageal mucosa (squammous) and gastric mucosa (columnar) moves proximally such that the lower part of esophagus now becomes lined with different types of gastric mucosa. This part of oesophagus has an increased risk for adenocarcinoma i.e.
Adenocarcinoma is seen in Barrets esophagus.

**45. Answer is E (Pernicious anemia is a risk factor):** *Harrison 18th/p 764 Harrison 17th/570, 571*

*Pernicious anemia is a risk factor for stomach carcinoma and not for esophageal carcinoma.*

**Esophageal carcinoma is more common in Men and in elderly**

Epidemiological feature of esophageal carcinoma

- *Men > Women (≈4 : 1)*
- *Predominantly affects older age group (> 50 years)*

**Adenocarcinoma is on the rise**
*For unclear reasons the incidence of squamous cell carcinoma has decreased while the rate of adenocarcinoma has risen dramatically. – Harrison*

**Dysphagia is the most common symptom**
*The most common presentation of esophageal carcinoma is progressive dysphagia (solids then liquids)*
*– Current Gastroenterology/301*

**46. Answer is A (Cisplatin):** *Harrison 18th/p 764 Harrison 17th/ 571; Bailey 23rd / 879; Bailey 24th/1015*

*Chemotherapy for esophageal cancer has improved considerably with the advent of regimens containing Cisplatin.*
*- Bailey*

*The best responses are seen in Squamous cell carcinomas.*

**47. Answer is A (Acute tubular necrosis)** : *KDT 5th/ 777*

*The most important toxity of cisplatinum is renal impairment – KDT 7th/777*
*Acute tubular necrosis is a manifestation of renal impairment and hence the answer.*

**48. Answer is A (Stomach) :** *Sabiston 16th / 744*

*After a portion of esophagus is removed, or after complete esophagectomy, a conduit must be established for alimentary continuity. The stomach, colon and jejunum have all been successfully used a esophageal substitutes but the Stomach appears to be the 'conduit' of choice because of ease in mobilization and its ample vascular supply – Sabiston*
**Colon** is used if the patient has undergone a partial or total gastrectomy previously, or if tumor involves the stomach to preclude a 5 cm margin.
**Jejunal loops** can also be used, but limited vascular supply restricts mobility.

## Stomach and Duodenum

### Peptic Ulcer Disease & H. Pylori Infection

**49. Answer is D (Pernicious anemia):** *Rubin's Pathology 5th/566; S. Das 3rd/818*

*Pernicious anemia is characterized by autoimmune destruction of parietal cells leading to hypochondria (↓ acid production). It is not associated with peptic ulcer disease.*

**Aetiological Factors in peptic ulceration**

| Primary Aetiologcial Factors (selected) | Associated Factors / Conditions (selected) |
|---|---|
| • *H. pylori infection*<br>• *NSAID's and other drugs eg. steroids*<br>• *Stress – Head injury / Burns*<br>• *Bile Reflux*<br>• *Smoking / Alcohol use*<br>• *Genetic Factors* | • *Endocrinal Disorders*<br>- *MEN*<br>- ***Primary Hyperparathyroidism***<br>- ***Zollinger Ellison Syndrome***$^{Q}$<br>- *Cushing's syndrome*<br>• ***Cirrhosis***$^{Q}$<br>• *Chronic Renal Failure*<br>• *Chronic Pulmonary Disease*<br>• *Chronic Paracreatic Disease*<br>• *Alpha 1 Antitrypsin deficiency* |

**50. Answer is C (Plummer Vinson Syndrome):** *Refer previous question*

*Plummer Vinson Syndrome is associated with dysphagia due to esophageal web and not with peptic ulcer disease.*

*Zollinger Ellison syndrome, Cirrhosis and smoking are all associated with Peptic ulcer disease.*

**51. Answer is B (High Acid Output):** *Harrison 18th/p 2441, 2442; 17th/1858; 'Textbook of Medicine' by Souhami 4th/777*

*Gastric ulcers are associated with normal or decreased gastric acid output. High Acid output is a feature of Duodenal Ulcers.*

*'Gastric acid output (basal and stimulated) tend to be normal or decreased in Gastric Ulcer Patient's'- Harrison*

**Aetiological factors in peptic ulceration:**

| Causal factor | Gastric ulcer | Duodenal ulcer |
|---|---|---|
| Hellicobacter pylori | Important | Very important |
| NSAIDs and aspirin | Important | Important |
| Acid | ***Normal or low acid output*** | ***High or normal acid output*** |
| Bile reflux | Important | Unimportant |
| Smoking | Important | Important |
| Stress | Evidence for head injuries and burns only | |
| Family history | Uncommon | Common |

**52. Answer is A (Curling's Ulcer):** *Harrison 18th/p 2457 Harrisons 17th/ 1869*

*Stress ulcers after severe burns are called curling's ulcers*

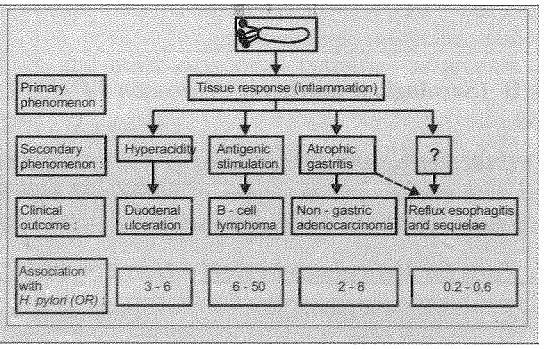
*Stress ulcers after head trauma : Cushing's Ulcers*
*Stress ulcers after severe burns : Curling's Ulcers*

**53. Answer is C (Gastric leiomyoma):** *Harrison 15th/961; Harrison 16th/ 1750, 887;Harrison 17th/1858, 1859 Harrison 18th/p 2442, 2443*

*Gastric leiomyomas are not associated with H. pylori infections*

**Diseases associated with H. Pylori infection**

1. Duodenal ulcer
2. Gastric ulcer
3. Chronic superficial gastritis
4. Chronic atrophic gastritis
5. Gastric adenocarcinoma
6. Lymphoproliferative disease (MALT)
7. Gastroesophageal reflux disease

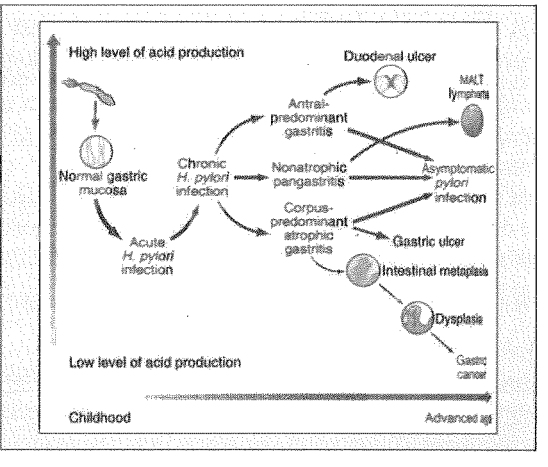



*MALT stands for Mucosa Associated Lymphoid Tissue Lymphoma*

**54. Answer is A (Antral predominant gastritis) :** *Harrison 16th/1750;Harrison 17th /946, 947 Harrison 18th/p 1262*

*The presence of antral predominant gastritis is associated with duodenal ulcer formation.*

| *Antral predominant gastritis* | *Corpus Predominant atrophic gastritis* | *Non atrophic pangastritis (chronic superficial gastritis)* |
|---|---|---|
| Duodenal ulcer | Gastric ulcer<br>Gastric adenocarcinoma | MALT Lymphoma |




**55. Answer is D (Fundal atrophic gastritis):** *Harrison 17th/946, 947; Harrison 18th/p 1262 Chandrasoma 2nd/ 565*

*Gastritis due to H. pylori infection is predominantly Antral, not fundal. Antral gastritis is associated with DU formation.*

*Gastritis involving the corpus is also seen and this predisposes to development of gastric ulcer, gastric atrophy and ultimately gastric carcinoma.* ***Fundal atrophic gastritis has not been mentioned.***

**56. Answer is D (SAFA test) :** *Harrison 14th / 942, 15th/960-61; 16th/887; 17th/947 (table-144.1) Harrison 18th/p 1263 (Table: 151.1)*

*SAFA test is not used for H.pylori infection*

***Diagnostic tests used for H pylori include:***

| Invasive | Non invasive |
|---|---|
| ***1. Endoscopy based Biopsy Urease test*** | ***1. Urea breath tests :*** |
| • Here specimen from antral biopsy are tested for "Urease".<br>• It is the most convenient endoscopy based test.<br>• It is *quick*[Q] and *simple*[Q] however it is neither fully sensitive nor fully specific | • Here patient drinks a labelled urea solution and blows into a tube.<br>• If H. Pylori urease is present, the urea is hydrolysed and labelled carbondioxide is detected in breath samples.<br>• It is thus a simple, safe test and cheaper than endoscopy |
| ***2. Histology :*** | ***2. Serological :*** |
| Here the biopsy specimen is subjected to histological examination.<br>It is *accurate*[Q], but time consuming | • Here specific IgG levels in serum are assessed.<br>• Does not differentiate between active and remote infection.<br>• Nevertheless it is particularly suited as an *epidemiological tool* |
| ***3. Culture :*** | ***3. Stool antigen test :*** |
| • Here the biopsy specimen is put in a culture medium.<br>• This is accurate [Q], and permits determination of antibiotic susceptiblities, but is also time consuming. | • New test appears less accurate than urea breath test<br>• Useful for follow up after treatment |

**57. Answer is B (Serological markers)** : *Harrison 14th/1599, 1600, 15th/961-962; 16th/Not elaborated; 17th/947 Harrison 18th/p 1263*

***An enzyme linked immuno-sorbant assay (ELISA) is the most commonly used serological method.***
*'Compared with endoscopic detection of H.Pyloric infection, ELISA has proved to be sensitive and specific and is* ***particularly suited for Epidemiological studies'.*** *– Harrison 14th/1600 (not mentioned in H - 16th).*

***Diagnostic Tests for Helicobacter pylori*** *– Harrison 14th*

| Test | Sensitivity | Comments |
|---|---|---|
| Serology | 95 | Does not differentiate between active and remote infection; epidemiologic tool; titer decreases slowly after eradication |
| Urease assay | | |
| Breath | 90-95 | Simple ; may be used to monitor therapy |
| Biopsy | 90-98 | Requires endoscopy |
| Histology | | Requires endoscopy; may be essential if antibiotic resistance emerges |
| Culture | 70-95 | Requires endoscopy'; may be essential if antibiotic resistance emerges |

**58. Answer is A (With chronic infection urease breath test becomes negative)** *Harrison 16th/887; 17th/946, 947 1858, 1859; Harrison 18th/p 1262, 1263, 2442, 2443 Microbiology by Greenwood 16th/294; Kumar&Clarke 5th/273*

*Urease breath test detects H. pylori infection by 'bacterial urease activity' and remains positive till the bacteria has not been eradicated with treatment.* ***Thus urease breath test becomes negative only after eradication of organism following treatment and not with chronic infection.***

- Despite a substantial humoral antibody response infection persists indefinitely (*persists life long if untreated*)
- Invasive diagnostic test are based on Endoscopic, endoscopy is a diagnostic application.
- *H. pylori produces several virulence factors that have been implicated in the damage of mucosa.*

**59. Answer is B (Urea breath test) :** *Harrison 16th / 1755, 887; Harrison 17th/947*

***The test of choice for documenting eradication is urea breath test. – Harrison 16th / 1755***

***Assessing success of Treatment / Eradicatiion of H. Pyrlori :***

- Assessment should be done atleast 4 weeks after completin of anti H. Pylori therapy.
- In the assessment of treatment success non invasive tests are normally preferred. – Harrison

**Assessment of success of treatment**

| Non invasive tests are preferred | Inasive tests are not preferred |
|---|---|
| **Urea breath test** : ***Test of choice for documenting eradication.***<br>**Stool antigen test** : *If UBT is not available a stool antigen test should be considered for documenting eradication* | **Biopsy based tests**<br>(Biopsy Urease test, Histology / Culture) *are invasive tests based on Endoscopic biopsy.* |
| **Serological testing** : Is **not useful for purpose of documentation of eradication** as antibody titres fall slowly and often do not become undetectable | ***These may be used to document eradication but are not preferred for this purpose.*** |

**60. Answer is A (Urease Breath Test):** *Harrison 16th/887,1755; 17th/946, 947 1858, 1859; Harrison 18th/p 1262, 1263, 2442, 2443 Microbiology by Greenwood 16th/294; Kumar &Clarke 5th/273 Harrison 16th / 1755, 887; Harrison 17th/947*

***The test of choice for documenting eradication is urease breath test.***

*Assessment of success of Treatment with Eradication of H. Pylori* should be done at least 4 weeks after completion of anti H. Pylori therapy. Non-invasive tests are typically preferred for assessment of Eradication. *The test of choice for documenting eradication is urease breath test. Urease breath test detects H. pylori infection by 'bacterial urease activity' and remains positive till the bacteria has not been eradicated with treatment. Thus urease breath test becomes negative only after eradication of organism following treatment and not with chronic infection.*

**61. Answer is A (Less prevalent in developing countries):** *Harrison 18th/p 1261, 1262 Harrison 17th/ 946, 947, 1859*

***H. pylori infection are more prevalent in developing countries.***

- The prevalence of H. pylori is approx. 30% in U.S. and other developed countries as against > 80% in most developing countries - *Harrison*
- H. Pylori is a gram negative, spiral, flagellated bacillus - *Harrison*
- Strains producing toxins (strains possessing cag pathogenicity DNA island) are more likely to give rise to severe gastritis, peptic ulceration and gastric cancer than strains without it.
  DNA island or cag pathogenicity island is a large region of DNA which has genes that control production of toxins.

| |
|---|
| Vacuolating toxin (VaC A) |
| Cytotoxin (cytotoxin associated gene - Cag A) |

- Urea breath test is a simple, inexpensive and consistently accurate test for H.pylori detection.

**62. Answer is B (The incidence of complications has remained unchanged):** *Answer of exclusion:Read text below*

- H. pylori eradication decreases the likelihood of occurrence of complications.
- The incidence of H.pylori is > 80% in most developing countries, and so the chances of reinfection are also high.
- H. pylori eradication reduced the chances of recurrence
- 'After successful eradication of H.pylori with antibiotics, ulcer recurrence rates are reduced dramatically to 5-20% at 1 year – CMDT 2003/571
- *Option 'b' 'The incidence of complications has remained unchanged' is thus the answer of exclusion !!*

**63. Answer is D (Erythromycin):** *Harrison's 15th / 962, 1657; 16th/889, 1754; 17th/949, 1863 Harrison 18th/p 1265, 2449*

***Erythromycin is not included in any of the successful multi drug regimens against H.pylori infection.***

| Indications of Treatment : |
|---|
| H-Pylori related duodenal and gastric ulceration |
| Low grade B cell MALT Lymphoma |

*H.pylori should be eradicated.*

**The most successful are the Triple and Quadruple multi-drug regimens:**

| Name | Drug 1 | Drug 2 | Drug 3 | Drug 4 |
|---|---|---|---|---|
| OCA | Omeprazole (20 mg BD) | Clarithromycin (500 mg BD) | Amoxicillin (1g BD) | |
| OCM | Omeprazole (20 mg BD) | Clarithromycin (500 mg BD) | Metronidazole (500 mg BD) | |
| OBTM | Omeprazole (20 mg BD) | Bismuth Subsalicylate (2 tabs QID) | Tetracycline (500 mg QID) | Metronidazole |

**64. Answer is A (Gentamycin):** *Harrison's 15th / 962, 1657; 16th/889, 1754; 17th/949, 1863 Harrison 18th/p 1265, 2449*

***Gentamycin is not used in any of the successful multi-drug regimens against H. Pylori Infection.***

**65. Answer is A (Oxytetracycline):** *Harrison 16th/1754; CMDT 2007/603*

*Oxytetrocycline has not been mentioned as a recommended agent for eradication of H. Pylori and hence is the single best answer of choice. Tetracycline and not Oxytetracycline forms part of the regimen.*
*Amoxycillin, Bismuth subsalicylate and Omeprozole have all been recommended for H. Pylori eradication*

| Recommended Regimens for Eradication of H. Pylori *(Harrison)* |
|---|
| **TRIPLE THERAPY** |
| 1. Bismuth subsalicylate plus Metronidazole plus Tetracycline |
| 2. Ranitidine bismuth citrate plus Tetracycline plus Clarithromycin or Metronidazole |
| 3. PPI plus Clarithromycin plus Metronidazole or Amoxicillin |
| **QUADRUPLE THERAPY** |
| PPI plus Bismuth subsalicylate plus Metronidazole plus Tetracycline |

*All PP1 are given twice daily except esomeprazolc (once daily)*

**Proton Pump inhibitiors (PPI) include:** Omeprazole (20mg), Lansaprazole (30mg) *Rabeprazole (20 mg), Pantaprazole (40 mg), Esmaprozole (40 mg)*

**66. Answer is B (Cisapride) :** *Harrison 18th/p 1264, 1265, 2449 Harrison 17th/ 948, 949, 1863; See previous question*

***Cispride is not included in any of the successful multidrug regimens against H. pylori infection.***

**67. Answer is D (Distal Duodenum):** *Harrison14th/1609, 15th/1663; (Harrison. 16th/1760; 17th 1869 – sites not elaborated) Harrison 18th/p 2457*

***Distal duodenum has not been mentioned on a site for cushing ulcers***

**Cushings ulcers**:

Are acute ulcers of the upper GI tract associated with intracranial injury or an *increase in intracranial pressure.*

| These ulcers my involve the |
|---|
| *Stomach* ϱ |
| *Proximal duodenum* ϱ |
| *Esophagus* ϱ |

**Complication :** Haemorrhage and perforation ϱ
**Treatment:** Correction of increased intracranial pressure + usual treatment of acute erosions and ulceration.

**Memo: *Curling's ulcers :*** *Stress ulcerations after severe burns – Robbins 7th/817*

**68. Answer is A (1st part of Duodenum) :** *Robbins 6th / 793; Robbins 7th/817*

***First part of duodenum is the most common site for peptic ulceration.***

| Sites in order of decreasing frequency : |
|---|
| 1. Duodenum, 1st portion ϱ |
| 2. Stomach, usually antrum ϱ |
| 3. At the gastro-esophageal junction, in the setting of gastroesophageal reflux ϱ |
| 4. Within the margins of a gastrojejunostomy ϱ |
| 5. In the duodenum, stomoch or jejunum of patients with Zollinger- Ellison Syndrome ϱ |
| 6. Within or adjacent to a Meckels diverticulum that contains ectopic gastric mucosa ϱ |

*Peptic ulcers are usually solitary lesions less than 4 cm in diameter*

**69. Answer is D (Lesser Curvature near incisura angularis):** *Schwartz 8th/956; Maningot's 10th/953; Textbook of Surgery by Jandra 3rd/95*

***The most common site of gastric ulcers (benign) is on the lesser curvature straddling the incisura angularis.***

**70. Answer is D (Haemorrhage):**

***The most common complication of both acute and chronic peptic ulcers is gastrointestinal haemorrhage.***

*'Haemorrhage is the commonest complication of chronic peptic ulcers'–Morson and Dawson's Gastrointestinal Pathology 4th/146*

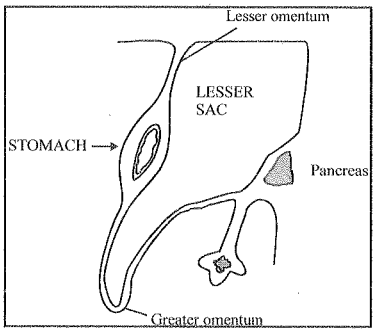
**71. Answer is B (Gastroduodenal Artery):** *Bailey 24th/1026; CSDT 11th/550*

***The most common arterial source of a hemorrhage in duodenal ulcers is the gastroduodenal artery.***

*'Bleeding ulcers in the duodenum are usually located on the posterior surface of the duodenal bulb. As the ulcer penetrates, the gastroduodenal artery is exposed and may become eroded.*
*Ulcers on the anterior surface of the duodenal bulb are not prone to bleed since no major blood vessels lie on the anterior surface of the duodenal bulb.'* – CSDT

**72. Answer is A (Omentum bursa) :** *Oxford text book of surgery 2nd/1302 Love & Bailey 23rd/911; BDC 23rd /194*

*"Gastric ulcers perforate into the lesser sac, which can be particularly difficult to diagnose" - Bailey*
*"A gastric ulcer perforates into the lesser sac, then no signs of generalised peritonitis can be seen but misleading symptoms may appear" - Schwartz*




As can be seen from the figure, a posteriorly perforating ulcer of the stomach will localize in the lesser sac or omental bursa only. *(lesser sacis synonymous with omental bursa)*

**73. Answer is D (Misoprostol is Drug of choice in pregnant patients)** *CMDT 2009/537; 2003/575; Katzung 8th/1068*

***Stimulant effect of Misoprostol on the uterus makes it contraindicated in women of child bearing age.***

- **The prostaglandin analogue misoprostol** is effective in the *prevention of NSAID induced gastric and duodenal ulcer*$^{Q}$ and is the *only agent approved by the FDA for this purpose.* $^{Q}$ *CMDT-2001/609*
- Misoprostol causes a dose dependent diarrhea and its *stimulant effect on the uterus makes it contraindicated in women of child bearing age*$^{Q}$*. Katzung 8th/1068*
- **$H_2$ receptor antagonist :** whereas previous recommendations were to administer these agents at least twice a day, a *single bed time dose may be just as effective and may elicit better compliance - Katzung*
  - For uncomplicated peptic ulcers, $H_2$ receptor antagonists may be administered twice daily or once daily at bed time, with equivalent efficacy- *CMDT 2001*
- **Proton pump inhibitors (Omeprazole) :** They are superior to $H_2$ receptor antagonists and to misoprostol in the healing of NSAID induced gastric ulcer.
  - Compared to $H_2$ Receptor antagonists, proton pump inhibitor provide faster pain relief and more rapid ulcer healing.
- **Alternate pharmacological approaches to failure of an $H_2$ blocker include :**
  - using a higher dose of the same $H_2$ blocker.
  - switching to another $H_2$ receptor antagonist
  - ***switching to a proton pump inhibiter*$^{Q}$ *(Omeprazole)***

**74. Answer is D (Highly selective vagotomy):** *Harrisons 17th/1866*

***Highly selective vagotomy is the procedure of choice for the management of chronic duodenal ulcers, except in situations where ulcer recurrence rates are high.***

Operations for duodenal ulcers:

| Operation/Procedure | Mortality | Recurrence rate (%) | Comments |
|---|---|---|---|
| Vagotomy and drainage | Intermediate | Intermediate | Selectively used |
| Highly selective vagotomy | Low (minimum) | ***High*** | Procedure of choice as it has the least complication rate |
| Vagotomy and antrectomy | *High* | ***Low (minimum)*** | Procedure with least recurrence rate.<br>Procedure of choice when recurrence is the major problem |

**75. Answer is A (Truncal vagotomy and antrectomy):** *Bailey Love 23rd/908*

***The question here strictly specifies recurrence as the major problem 'Recurrent duodenal ulcer'.***
*Hence a procedure with the minimum recurrence rate, would logically be, the best operation.*
***Truncal vagotomy and antrectomy are associated with minimum recurrence rate and is the answer of choice.***

**Note:**

| Operation with maximum reduction in acid production | Operation with minimum operative mortality | The most widely used procedure in India |
|---|---|---|
| Truncal vagotomy and antrectomy | Highly selective vagotomy | Truncal vagotomy plus a drainage procedure *Gastrojejunostomy is at present the most widely used procedure.* |

**Highly selective vagotomy:**

- In highly selective vagotomy nerves of Latarjet supplying the antrum are preserved. $^{Q}$
- A drainage procedure is not required $^{Q}$
- Operation mortality is lower than in any other definitive operation for duodenal ulceration. $^{Q}$

**76. Answer is C (Vagotomy + Antrectomy) :** *Repeat*

***Vagotomy with Antrectomy is associated with lowest recurrence rates.***

**77. Answer is B (Presence of Hypertonic Contents in small intestine) :** *Love & Bailey 23rd / 913; Sabiston 16th / 853; Harrison 14th / 1608, 15th/1660*

DUMPING SYNDROME refers to a syndrome of abdominal and vasomator symptoms which results from dumping of food stuffs with a high osmotic load, from the stomach, into the small bowel.

*Loss of storage capacity of stomach and ablation, by pass or destruction of pylorus, results in rapid emptying of hyperosmolar chyme into duodenummm and small intestine*. Extracellular fluid then shifts into the intestinal lumen to restore isotonicity resulting in decreased intravascular volume, which gives rise to the vasomotor symptoms.

***Note*** that while reduced gastric capacity contributes, option (b) is a more accurate answer.

Dumping Syndrome is actually of two types:

- **Early dumping syndrome** (as described above)
- **Late dumping syndrome:** This is *Reactive hypoglycemia*$^{Q}$. The carbohydrate load in thesmall intestine later causes a rise in plasma glucose, which in turn causes insulin levels to rise causing a secondary hypoglycemia.

**78. Answer is D (Surgery is usually indicated) :** *Harrison 14th / 1608; Harrison 15th/1660*

***There is no role of surgery in management of post cibal syndromes.***

Both types of postcibal syndrome are treated by dietary measures including:
- limitation of sugar containing liquids and solids,
- elimination of liquids at meal time, and
- eating of frequent small meals.

In severe cases, symptoms may improve, with the somatostatin-analogue *Octreotide*.
There is *no role of surgery* in management of post cibal syndromes.

## Gastric Outlet Obstruction

**79. Answer is B (Duodenum) :** *Bailey 23rd / 917 ; Repeat*

***Gastric outlet obstruction in a patient with peptic ulcer disease is suggestive of pyloric stenosis.***
***The term pyloric stenosis is normally a misnomer. The stenosis is seldom at the pylorus.***
***Commonly the stenosis is found in the first part of the duodenum, the most common site for a peptic ulcer.***

**80. Answer is B (The pyloric tumor is best felt during feeding):** *Bailey Love 23rd /899*

- First born male child is characteristically most commonly affected
- It is four times more common in males as in females
- The condition does not present at birth. It is most commonly seen 4 weeks after birth

**Presentation**

- Vomiting is the presenting symptom (child vomits milk and *no bile is present*[Q])
- ***Immediately after vomiting the child is hungry i.e. loss of appetite does not occur.***
- Weight loss is striking and rapidly the infant becomes emaciated and dehydrated.
  However, greater awareness of pyloric stenosis has led to earlier identification of patients and hence with ***fewer incidences of chronic malnutrition and severe dehydration*** - *Nelson 10th/1130*
- The ***diagnosis is usually made with a test feed*** : In this the baby is fed with the bottle by a nurse or mother and surgeon :

  ***- palpates the abdomen with a warm hand to detect the lump***

  - observes the characteristic peristatic waves pass across the upper abdomen.
- *Pathologically musculature of pylorus adjacent to antrum is grossly hypertrophied*
- *Ultrasonography is the investigation of choice*
- *Hyperchloremic alkalosis is common and following diagnosis first concern is to correct metabolic abnormalities - child is rehydrated with dextrose saline & potassium*[Q]
- *Treatment of choice : Ramsted's operation - 'Pyloromyotomy'*

**81. Answer is B (Hypochloremic alkalosis) :** *Bailey Love 22nd/674, 23rd/899*

***The vomiting of hydrochloric acid results in hypochloremia and alkalosis i.e. hypochloremic alkalosis***[Q]

- Characteristically *first born male infant*[Q] is most commonly affected (Males > Females) [Q]
- *Onset of symptoms*, has its, peak incidence *between the third & sixth weeks of life*[Q] and *it is almost never present at birth* [Q].
- *Most common presenting symptom is vomiting*[Q] & accounts for the *hypochloremic alkalosis.* [Q]
- *The procedure of choice is a Halsted's operation*[Q] & not a Heller's myotomy.
  *- Heller myotomy is the procedure of choice for achalasia cardia.*[Q]

**82. Answer is C (Metabolic alkalosis with paradoxical aciduria) :** *Bailey 23rd / 917*

The vomiting of hydrochloric acid results in hypochloremia and alkalosis i.e. *hypochloremic alkalosis*[Q]
Initially the urine has a low chloride and high bicarbonate content reflecting the primary metabolic abnormality. *This bicarbonate is excreted along with sodium and so with the time the patient becomes progressively hyponatremic and more profoundly dehydrated.* ***Because of the dehydration a phase of sodium retention follows and potassium and hydrogen ions are excreted in preference. This results in urine being paradoxically acidic, and hypokalemia ensues.***

**83. Answer is C (Hypokalemia) :** *Harrison 14th/ 230, 15th/288-89, 279; Harrison 16th/259, 264*

***Loss of gastric secretions results in Hypokalemia.*** *Loss of gastric contents results in volume depletion and metabolic alkalosis both of which promote kaliuresis. (Leads to hypokalemia)*

**Repeated vomitings may have many deleterious effect**:

| Due to process of vomiting | Metabolic | Nutritional |
|---|---|---|
| • Pressure Rupture of esophagus [Q] : *Boerhaave's syndrome* [Q]<br>• Linear mucosal tears in the Region of cardioesophageal junction with resultant hemetemesis- *Mallory weiss syndromes* [Q] | • Dehydration<br>• Loss of gastric secretions (specially HCl, $K^+$ ions) Resulting in ***Metabolic Alkalosis and Hypokalemia*** [Q]<br>• *$HCO_3^-$ level will be increased* (as the person is having metabolic alkalosis)<br>• *Hypochloremia* (due to loss of HCL) | • Malnutration<br>• *Dental caries* [Q] |

*Aspiration Pneumonitis may be seen in the unconscious.*

**84. Answer is B (Normal saline):** *Harrison 16th/254*

*The patient in question has developed dehydration with mild hyponatermic dehydration with hypokalemia.* ***Isotonic normal saline (.9%NaCl) is the solution of choice for intravenous replacement therapy.*** *Hypokalemia should be corrected by adding appropriate amounts of KCl to the replacement solution. – Harrison*

**Management of hypovolemia with intravenous therapy:**

**Mild losses**
Oral correction with water and sodium salts

**More severe hypovolemia**
↓
Intravenous therapy

Patients with loss of water and electrolytes
↓

| Normonatremic Mildly hyponatremic | Severe hyponatremia | Hypernatremia |
|---|---|---|
| Isotonic normal saline (0.9% NaCl) | Hypertonic saline (3% NaCl) | Hypotonic solutions (0.45% NaCl half N.S), (5% dextrose) |

Patients with significant haemorrhage or anemia

- Blood transfusion is treatment of choice
- Colloid containing solutions are a substitute

**85. Answer is D (Hypertrophic Pyloric Stenosis) :** *Refer text*

***Ramstedt's extramucosal pyloromyotomy is used for the treatment of infantile hypertrophic pyloric stenosis.***

**86. Answer is A (GERD):** *Refer text*

***Nissen fundoplication is a surgical procedure to treat Gastroesophageal Reflux Disease (GERD) and Hiatus Hernia.***

## Menetrier's disease

**87. Answer is B (Exophytic growth):** *Harrison 18th/p 2459 Harrison's 17th/1871, 1872; Current Surgical Diagnosis and Treatment 12th/535,536*

***Menetrier's disease is characterized by hypertrophy of gastric mucosa and not by exophytic growth.***

**Menetrier's disease**

Menetrier's disease is a relatively rare disorder of the stomach characterized by large tortuous mucosal folds

**Etiology**

- Etiology is unknown
- Over expression of growth factors such as TGF are suggested

**Pathology**

Gross
- Marked Hypertrophy of gastric folds/Rugae$^{Q}$
- Hypertrophy results from hyperplasia of mucus producing cells (mucosa)$^{Q}$
- Hypertrophy is most prominent in the body and fundus $^{Q}$

Histological/microscopic
- Massive foveolar hyperplasia (Hyperplasia of surface and glandular mucosal cells).
- Pits of gastric glands elongate and may become tortuous
- Lamina propria may contain a mild chronic inflammatory infiltrate
  (Note: Although lamina propria may contain an inflammatory infiltrates, Menetrier's disease is not considered a form of gastritis

**Clinical picture**

- Protein losing enteropathy is characteristic
  Excessive protein is lost from the thickened mucosa into the gut which results in hypoprotenemia and edema
- Gastric acid secretion is usually reduced or absent
  This happens because mucosal cell hyperplasia replaces most of the parietal cells.
- Epigastric pain accompanied by nausea, vomiting anorexia and weight loss

Overt bleeding is unusual but occult gastrointestinal bleeding may occur

**Differential Diagnosis**

DD includes conditions that may present with large gastric folds:
ZES
Malignancy
Infiltrative disorders eg sarcoidosis
Infectious etiology (CMV, Histoplasmosis, syphilis)

**Prognosis**

These is an increased risk of adenocarcinoma of stomach in adults with menetrier's disease (CSDT)

**88. Answer is B (Usually increased acid secretion):** *Harrison 18th/p 2459 Harrison's 17th/1872; Refer previous question*

***Gastric acid secretion is usually reduced or absent (and not increased)***

*Gastric acid secretion is usually reduced or absent because of replacement of paricta cells' Harrison's*

*Menetrier's disease carries an increased risk of developing adenocarcinoma of stomach (premalignant) is associated with a protein losing enteropathy and may be confused with Zollinger Ellison Syndrome as ZES also presents with large gastric folds.*

## Carcinoma Stomach

**89. Answer is D (Intestinal metaplasia Type III):** *Harrison 15th/580; 16th/525; 17th/ 572; Harrison 18th/p765, 766 Robbins 7th/823*

| **Risk factors for stomach carcinoma :** |
|---|
| 1. Long term ingestion of high concentration of nitrates in dried smoke and salted foods. Q |
| 2. Loss of gastric acidity - atrophic gastritis Q<br>- partial gastrectomy (peptic ulcer surgery) Q<br>- pernicious anemia Q |
| 3. Infection with H. pylori Q |
| 4. Intestinal metaplasia Q |
| 5. Gatric ulcer & polyps Q - (Q **No association has been found between deodonal ulcer and gastric cancer)** |
| 6. Menetrier's disease Q : extreme hypertrophy of gastric rugal folds. |
| 7. Blood group A Q |
| 8. Cigarette smoking, Dust ingestion, Ingestion of spirits, Genetic factors have also been implicated. |

**90. Answer is C (Hiatus Hernia):** *Gastrointestinal and Liver Diseases by Feldman, Freidman 8th/1147, 1148*

***Hiatus Hernia is not considered a premalignant lesion for gastric carcinoma.***

| Premalignant lesions for Gastric Adenocarcinoma |
|---|
| • Chronic Atrophic Gastritis (H. pylori > Pernicious Anemia) |
| • Intestinal Metaplasia Type II and Type III<br>*(Intestinal Metaplasia type I is not associated with increased risk)* |
| • Gastric Dysplasia |
| • Gastric polyps (Adenomatous polyps)<br>*(Hyperplastic polyps are generally not considered premalignant as the rate of malignant transformation in these polyps is <1% and confined to polyps > 1cm)* |
| • Previous Gastrectomy |
| • Menetrier's Disease |
| • Gastric ulcers (long standing gastric ulcers : Low risk) |

**91. Answer is B (Hyperplastic Polyps):** *Harrison 18th/p 766 Harrison 17th/572; Robbins 7th/823; Manual of Oncology 6th/193; Internal Medicine 5th/2046, 2047*

***'Hyperplastic polyps do not appear to have malignant potential'*** *– Manual of Oncology 6th/193*

**Gastric Polyps and Premalignant Potential**

| Hyperplastic Polyps | Adenomatous Polyps |
|---|---|
| • Hyperplastic Polyps account for >75% of all gastric polyps | • Adenomatous Polyps account for < 25% of all gastric polyps |
| • These are not considered premalignant lesions and do not appear to have any significant malignant potential (< 1%) | • These are considered premalignant lesions They are most commonly found in the antrum of stomach and have significant malignant potential |

**92. Answer is C (Duodenal Peptic ulcer):** *Refer previous question*

***Gastric adenocarcinoma may be associated with long standing gastric peptic ulcers (small risk) but not with duodenal ulcers.***

*Atrophic gastritis, partial gastrectomy and blood group A have all been included in the list of risk factors for gastric adenocarcinoma.*

**93. Answer is C (Intestinal metaplasia):** *Harrison 16th/525*

*Intestinal metaplasia is the most significant risk factor for development of gastric cancer amongst the options provided.*

*"The risk of tumor development is greatly increased in patients in whom mucosal inflammation progresses to multifocal mucosal atrophy and intestinal metaplasia"- Robbins*

*'Serial endoscopic examinations of the stomach in patients with atrophic gastritis have documented replacement of the usual gastric mucosa by intestinal type cells. This process of intestinal metaplasia may lead to cellular atypia and eventual neoplasia.' - Harrison*

**94. Answer is A (Antrum):** *CSDT 11th/557*

*The most common site of gastric adenocarcinoma is antrum*

*'40% tumors are in the antrum, predominantly on the lesser curvature, 30% arise in the body and fundus, 25% at the cardia and 5% involve the whole organ'- CSDT*

**95. Answer is D > C (Fundus> Body):** *Sleisenger & Fordtrans text book of Gastrointestinal disease 7th/813; An Atlas of Gastroenterology by Kapadia 1st (2002)/58; Current Gastroenterology 2nd/391*

*Atrophic glands with extensive intestinal metaplasia are most charachteristically confined to the fundus in patients with pernicious anaemia.*

*Pernicious anemia is associated with autoimmune atrophic gastritis affecting the fundic glands.Intestinal metaplasia (premalignant for gastric carcinoma),is charachterstically seen in this area of atrophic gastritis* ***.Atrophic glands with extensive intestinal metaplasia are most charachteristically confined to the fundus in patients with pernicious anaemia.Gastric cancer in case of pernicious anemia is most often located in the fundus or body of the stomach rather in the Antrum.***

| Gastric cancer secondary to: | Location / Site |
|---|---|
| H. pylori | Antrum > body > fundus |
| Pernicoius Anemia | Fundus and body (not antrum) |

**96. Answer is C (Gastric adenocarcinoma confined to mucosa and submucosa):** *Harrison 18th/p 765, 766 Harrison 17th/571, 572; Robbins 7th/824*

*Early gastric carcinoma is defined as a lesion confined to the mucosa and submucosa regardless of the presence or absence of perigastric lymphnode metastasis – Robbins*

**97. Answer is C (Involvement of mucosa, submucosa and muscularis) :** *Harrison 18th/765, 766; 17th/571, 572 Bailey 23rd / 922; Robbins 7th/824*

| | |
|---|---|
| *Early gastric cancer:* | Cancer limited to the mucosa and submucosa with or without lymph node involvement. |
| *Late gastric cancer :* | Cancer involving the muscularis. |

**98. Answer is A (Superficial spreading type) :** *Robbins 6th / 800 ; Bailey 22nd / 963; Bailey 23rd / 920, 921*

*Superficial spreading type indicates an early stage of type II malignancy. It is therefore potentially curable, and thus has the best prognosis amongst the choices provided*

In Ca Stomach, three macroscopic growth patterns are recognized, and may be evident in both early and advanced gastric cancer stages :

a. Exophytic (Type I) : Protruded in early stages, Cauliflower like polypoidal growth in advanced stages.

b. Flat or depressed (Type II) : With no obvious tumor mass in mucosa eg. Superficial spreading type

c. Excavated arc Ulcerated (Type III) : Shallow or deeply erosive crater is present in the wall of stomach.

***Early cases of type I & type II are potentially curable*** - *Bailey 22nd / 693*

The prognosis depends on depth of invasion and extent of nodal and distant metastasis.

***Superficial spreading type indicates an early stage of type II malignancy. It therefore is potentially curable, and thus has the best prognosis amongst the choices provided.***

***The best answer therefore is superficial spreading type which indicates an 'Early Gastric Cancer'.***

***'Linitis plastica'*** is characterized by ***extensive infiltration of malignancy*** into a broad region of gastric wall or entire stomach creating a rigid, thickened *leather-bottle like stomach.*

**99. Answer is C (Partial Gastrectomy + Distal pancreatectomy):** *NSSG (National Site Specific Group) Guidelines for Upper GI Cancers (NHS, UK) Official publication; 'Complications in Surgery' by Doherty (Lippincott) 2006 /398 'Diagnosis and Management of Cancer' by Mehta & Bansal (Jaypee) 1st/363; Sabiston 18th/1265*

***Partial gastrectomy with distal pancreatectomy should be adequate to manage this distal gastric tumor with direct invasion into the distal pancreas.***

*Tumors of the distal third / antrum of stomach require a subtotal gastrectomy (Partial gastrectomy). The distal pancreas should be removed as there is direct invasion of the distal pancreas. Splenectomy is not indicated as the tumor does not directly invade the spleen, and involvement of splenic hilar lymph nodes is unlikely as the tumor is located in the distal third of the stomach (and not in the proximal stomach). This patient is best managed by subtotal gastrectomy + lymphadenectomy + distal pancreatectomy.*

**Guidelines for management of Gastric carcinoma**

- Surgical resection remains the mainstay of treatment of gastric cancer either for cure or for palliation
- ***The extent of gastric resection*** depends on the site of tumor in the stomach.
  *Tumors in the distal third or antrum of stomach require a subtotal gastrectomy (partial gastrectomy) while tumors of the middle or proximal third of the stomach require a total gastrectomy*

| *Distal Third /Antrum Gastric cancer* | *Middle Third / Proximal Gastric cancer* |
|---|---|
| *Subtotal Gastrectomy* | *Total Gastrectomy* |

*Patients with curable cancers of the stomach should also undergo a D2 lymphadenectomy*

- ***The extent of resection of adjacent* structures (pancreas, spleen etc)** depends on the location of primary tumor and local invasion

*Pancreatic Resection*

The distal pancreas should not be removed a part of a resection for a cancer of the distal two third of the stomach (unless there is direct invasion)

The distal pancreas should be removed only when there is direct invasion and still a chance of a curative procedure in patients with carcinoma of the proximal stomach

*Splenic resection*

*Splenectomy is not indicated unless the tumor directly invades the spleen or involves the splenic hilar lymph nodes.* Resection of spleen and splenic hilar lymph nodes *may be considered* in patients with *tumors of the proximal stomach* located in the greater curvature / posterior wall of the stomach close to the splenic hilum *where the incidence of splenic hilar nodal involvement is likely to be high*

*Splenic hilar lymph nodes are generally not involved in distal third / antral gastric cancers*

| Adjacent structure | Distal Third / Antrum Gastric cancer | Proximal Gastric cancer |
|---|---|---|
| *Pancreas* | • *Should not be removed routinely*<br>• *Resected if there is direct invasion* | • *Should not be removed routinely*<br>• *Resected if there is direct invasion and/or still a chance of curative procedure* |
| *Spleen* | • *Should not be removed routinely*<br>• *Resected if there is direct invasion or involvement of splenic hilar lymph nodes (This is unlikely)* | • *May require splenectomy to include the draining lymph nodes especially if lesion is located on the greater curvature / posterior wall, close to the splenic hilum* |

**100. Answer is A (Stomach) :** *Bailey 21st / 892; Not elaborated in later editions*

*The most common benign neoplasms of the stomach are Leiomyomas* ♀.
'Despite the fact that small bowel represents 75% of the length of Alimentary tract, *its tumors are less common than those in the stomach'.*
***These statements lead us to the conclusion that** within the GIT leiomyomas are more common in stomach than in other parts.*

## Malabsorption Syndrome and Disorders of Small Intestine

### General

**101. Answer is D (Tangier's Disease):** *Refer text below*

***Tangier's Disease is not a malabsorption syndrome.***
*Whipple's Disease, Celiac sprue and Tropical sprue are charachteristic / typical examples of malabsorption syndromes.*

**Tangier's Disease** *is a genetic disorder charachterized by a severe deficiency of high density lipoprotein cholesterol (HDL-C) concentration in the plasma as well as deposition of cholesterol crystals in the tissue. Tangier's disease is synonymous with* ***Familial High Density Lipoprotein Deficiency.***

**Malabsorption Syndromes**

| Diffuse, specific | Patchy, specific | Diffuse, nonspecific |
|---|---|---|
| • *Whipple's disease* | • *Intestinal lymphoma* | • *Celiac sprue* |
| • *Agammaglobulinemia* | • *Intestinal lymphangiectasia* | • *Tropical sprue* |
| • Abetalipoproteinemia | • *Eosinophilic gastroenteritis* | • *Bacterial overgrowth* |
| | • *Amyloidosis* | • *Folate deficiency* |
| | • *Crohn's disease* | • *Vitamin B12 deficiency* |
| | • *Infection by one or more microorganisms* | • *Radiation enteritis* |
| | • *Mastocytosis* | • *Zollinger – Ellison syndrome* |
| | | • *Protein –calorie malnutrition* |
| | | • *Drug-induced enteritis* |

**102. Answer is A (Steatorrhea):** '*Differiential Diagnosis in Medicine: From Symptom to Diagnosis (Thieme) 2007/821*

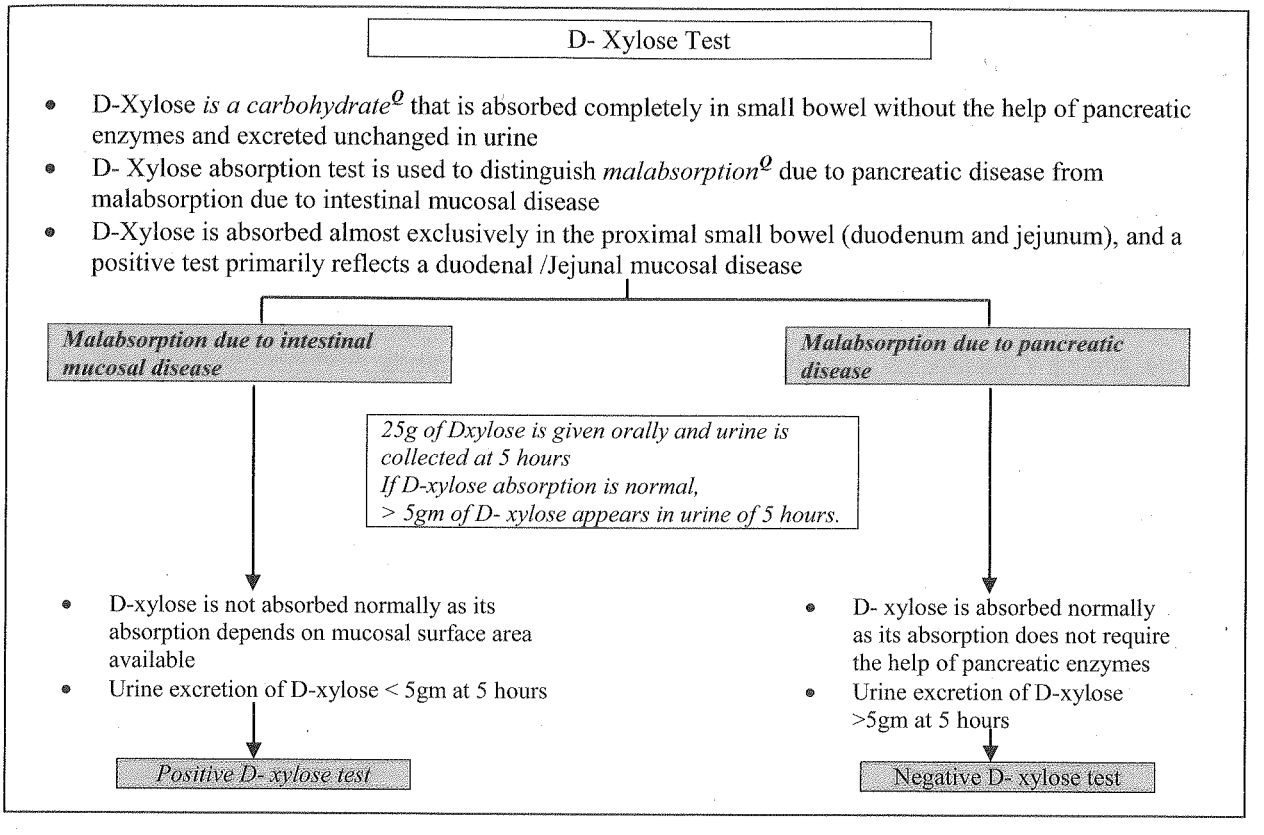
***Malabsorbtion of fat soluble vitamins is typically seen in steatorrhea and pancreatic exocrine deficiency (not pancreatic endocrine deficiency).***

***Steatorrhea** is typically defined as increased excretion of fat in stool (excretion of > 7.0 gm of fat in stool during 24 hours while the patient is on a diet containing no more than 100gm of fat per day).*
***Steatorrhea essentially represents malabsorption of fat.***

This may be caused by several conditions including:
- *Acute or chronic Liver disease / Biliary Disease*
- *Mucosal disease (eg. Celiac disease / Crohn's disease)*
- *Reduced absorptive surface (Small Bowel Syndrome)*
- *Reduced contact time (Laxative abuse, Carcinoid syndrome)*
- *Disturbed mesenteric blood supply (Mesenteric ischemia)*
- *Disturbed mesenteric lymphatic drainage (Tuberculosis, Malignancy)*
- ***Pancreatic exocrine deficiency (Reduced Pancreatic Lipase)***

**103. Answer is A (D-xylose test):** *Harrison 18th/2467; Harrison 17th/1878*

*D-xylose is a carbohydrate that is absorbed almost exclusively in the proximal small bowel without the help of pancreatic enzymes. A positive D-xylose test indicates malabsorption due to intestinal mucosal disease and thus be used as a test for assessment of mucosal function.*




**104. Answer is A (Pancreatic insufficiency):** *Refer text below Harrison 18th/p 2467, 2470 Harrisons 17th / 1878, 1881, Manual of Gastroenterology 4th/ 213*

***Pancreatic insufficiency is associated with a Negative D- xylose test (Normal D-xylose excretion)***

**105. Ans is A (Carbohydrate malabsorption due to mucosal disease):** *Harrison 16th/1769; 17th/1878; 18th/p 2467*

***'The urinary D-xylose test for carbohydrate absorption provides an assessment of proximal small intestine mucosal function.'*** *– Harrison 16th/1769*

**Urinary D-xylose test:**

**Principle :**
D-xylose is a 'pentose' that is completely absorbed almost exclusively in the proximal small intestine and excreted subsequently in the urine. The level of excreted D-xylose in urine is estimated.
Any decrease in its level in urine means abnormality in carbohydrate absorption in proximal intestine.

**Procedure & interpretation**
25g D-xylose is given and urine is collected for 5 hrs.
An excretion of < 4.5g primarily reflects the presence of duodenal / jejunal mucosal disease.

**106. Answer is C (D-xylose test) :** *Harrison 14th/1620, 15th/1672, 1634, 1674 t; 16th/1769; 17th/1878; Harrison 18th/2467*

***D-xylose absorption test*** *is the most commonly employed test for carbohydrate absorption - Harrison*
*An endoscopic mucosal biopsy is the more specific test and is now considered essential.*
***As endoscopic small intestinal biopsy' is not provided in the options 'D-xylose test' is the answer of the choice***

**Evaluation of small intestine malabsorption of carbohydrates due to altered small intestinal mucosal function**

| | |
|---|---|
| **Urinary D-xylose test** | Non invasive test of choice |
| **Endoscopic mucosal biopsy** | Test of choice / preferred test |

*'The ease of obtaining a mucosal biopsy of the small intestine by endoscopy and the false negative rate of the Dxylose test have led to its diminished use. When small intestinal disease is suspected, a small intestinal biopsy should be performed' – Harrison*

**107. Answer is D (Celiac sprue) :** *Harrison's Gastroenterology & Hepatology 1st/165*

***A Positive d-xylose test suggests a diagnosis of celiac disease***

*Decreased urinary excretion of d- xylose (<5.0 gm) 5 hours after administration of 25 gm D- xylose (positive test) suggests malabsorption due to intestinal mucosal disease in the proximal small bowel (duodenum and jejunum).*

***Celiac disease is a charachteristic cause for positive d-xylose test and the single best answer amongst the options provided***

*Modestly abnormal d-xylase test may also be seen in cases of bacterial overgrowth syndrome, however patients with bacterial overgrowth syndrome may also have normal d-xylose excretion, and hence this is not considered as the most likely diagnosis*

| | D-Xylose Test | Schilling Test | Duodenal Mucosal Biopsy |
|---|---|---|---|
| Chronic pancreatitis | Normal | 50% abnormal; if abnormal, normal with pancreatic enzymes | Normal |
| Bacterial overgrowth syndrome | Normal or only modestly abnormal | Often abnormal; if abnormal, normal after antibiotics | Usually normal |
| Ileal disease | Normal | Abnormal | Normal |
| Celiac sprue | Decreased | Normal | Abnormal: probably "flat" |
| Intestinal lymphangiectasia | Normal | Normal | Abnormal: "dilated lymphatics" |

**108. Answer is D (Celiac sprue):** *Refer text below manual of Gastroenterology 4th/ 213*

***Celiac sprue is associated with a positive D- xylose and not a False positive D-xylose test.***

D-xylose Test

| Positive test | False positive test |
|---|---|
| *Decreased (↓) D- Xylose excretion in urine due to malabsorption from gastrointestinal mucosal disease* | *Decreased D-xylose excretion in urine due to causes other than malabsorption from small bowel mucosal disease* |
| Causes Include | Causes Include |
| • ***Celiac disease*** <br>• *Tropical sprue* <br>• *Whipple's disease* <br>• *Other mucosal diseases* | • ***Bacterial overgrowth*** <br>• ***Renal insufficiency*** <br>• *Delayed gastric emptying* <br>• *Rapid intestinal transit* <br>• *Vomiting* <br>• ***Ascites /Pleural Effusion*** *(Third space collections)* |

*After a positive D-xylose test is obtained, a jejunal biopsy should be performed to diagnose the mucosal abnormality.*

**Blood loop syndrome** may be associated with a reduced functional intestinal mucosa and bacterial overgrowth. This condition may thus lead to both, a positive or false positive D- xylose test depending on the pathophysiology involved.

**109. Answer is E (All of the above):** *Refer previous question; Manual of Gastroterology 4th/213*

***Blind loop syndrome*** and *Antibiotic therapy may cause false positive D-xylose test due to* ***bacterial overgrowth***
*Pyloric stenosis may cause false positive results due to* ***delayed gastric emptying and persistant vomiting.***
*Ascitis is an established cause for false positive D- xylose test due to large collection of fluid in third space*

**110. Answer is A and C (Abnormal in pernicious anemia; Abnormal in ileal disease):** *Harrison 18th/p 2467* Harrison *17th/1878*

***Schilling test is abnormal in conditions that affect cobalamine absorption including Pernicious anemia, Chronic Pancreatitis, Bacterial overgrowth syndrome and Ileal dysfunction.***

| Conditions with Abnormal Schilling's Test (Abnormal Cobalamine Absorption) |
|---|
| ***Pernicious anemia*** |
| ***Chronic Pancreatitis*** |
| ***Achlorhydria*** |
| ***Bacterial overgrowth syndrome*** |
| ***Ileal dysfunction*** |

**Schilling Test:**

- Schilling test is performed to determine the cause of cobalamine malabsorption.
- Since cobalamine absorption requires multiple steps including gastric, pancreatic and ileal processes, the Schilling test can also be used to assess the integrity of these other organs.
- The Schilling test is performed by administering Co58-labeled cobalamin orally and collecting urine for 24h
- The ***Schilling test may be abnormal (defined as less than 10 percent excretion in 24h) in conditions that affect cobalamine absorption including Pernicious anemia, Chronic Pancreatitis, Bacterial overgrowth syndrome and Ileal dysfunction***
- The etiology for an abnormal Schilling test may be deduced by administering Co58-labeled cobalamin with intrinsic factor, pancreatic enzymes or after 5 day course of antibiotics.Differential Results of Schilling Test in various diseases associated with cobalamin malabsorption may thus help establish the diagnosis.

| Diagnosis | $^{58}$Co-Cbl | With Intrinsic Factor | With Pancreatic Enzymes | After 5 Days of Antibiotics |
|---|---|---|---|---|
| Pernicious anemia | *Reduced* | *Normal* | *Reduced* | *Reduced* |
| Chronic pancreatitis | *Reduced* | *Reduced* | *Normal* | *Reduced* |
| Bacterialovergrowth | *Reduced* | *Reduced* | *Reduced* | *Normal* |
| Ileal disease | *Reduced* | *Reduced* | *Reduced* | *Reduced* |

**111. Answer is D (13C Triclosan): Pediatric Drug Development:** *Concepts and Applications (John Wiley & Sons, 2011)/81; '13C–Breath Tests in Medical Research and Clinical Diagnosis (http://www.fan-gmbh.de/docs/13c-breathtests.pdf)*

***Triclosan is not used for the evaluation of fat malabsorption.***

*Triclosan is an antibacterial and antifungal agent found in numerous consumer products, including soaps, detergents, toys, and surgical cleaning treatments. Its efficacy as an antimicrobial agent and the risk of antibacterial resistance remains controversial.*

**Breath tests using 13 C-marked triglycerides** are based on the principle that intestinal triglyceride absorption requires prior hydrolysis by lipase to produce free fatty acids and monoacylglycerol. These metabolites are incorporated into micelles, absorbed, resynthesized and transported to the liver. Lipolytic hepatic enzymes subsequently release 13 C-marked fatty acids. These undergo Beta-oxidation which results in formation of 13 CO2 that is absorbed into the bloodstream, transported to the lung and exhaled. The increase in 13 CO2 concentration in breath thus correlates with intestinal lipid digestion and absorption. *13C-marked triglycerides are nonradioactive and can be applied safely and repeatedly, also to children and pregnant women.* Initially focused on investigating infants and pregnant women with their particularly high risks of being exposed to energy rich radiation, breath tests using the stable isotope 13C *instead of its radioactive counterpart 14C*, nowadays have replaced 14C-breath tests almost completely.

| | |
|---|---|
| [13C]TRIOCTANOIN BREATH TEST | 13C trioctanoin breath test is used for studying fat absorption, particularly with respect to medium chain fatty acids. Suitability for clinical diagnosis: good. |
| [1-13C]TRIOLEIN BREATH | 13C triolein breath test is used for studying fat malabsorption and aetiology of steatorrhea, particularly with respect to long chain fatty acids. Suitability for clinical diagnosis: satisfactory. |
| 13C]TRIPALMITIN BREATH TEST | The [13C]tripalmitin breath test is used for studying fat malabsorption and aetiology of steatorrhea, particularly with respect to long chain fatty acids. Suitability for clinical diagnosis: satisfactory. |

Other 13C- breath tests for investigating exocrine pancreatic function and diagnosing pancreatic diseases include

- 13C- CHOLESTERYL OCTANOATE BREATH TEST
- 13C-CHOLESTERYL OLEATE BREATH TEST
- 13C-LINOLEIC ACID BREATH TEST; 13C-LINOLENIC ACID BREATH TEST
- 13C OLEIC ACID BREATH TEST; 13C-PALMITIC ACID BREATH TEST; 13C-STEARIC ACID BREATH TEST
- 13C-HIOLEIN BREATH TEST ;
- 13C-TRIGLYCERIDE BREATH TESTS with genuine plant oils and other genuine triglycerides
- 13C-TRILINOLEATE BREATH TEST

**112. Answer is A (Intrinsic factor deficiency):** *Repeat*

Shilling's test is typically done to determine the cause of cobalamine malabsorption (Vitamin B12 malabsorption) ***Vitamin $B_{12}$ absorption (Schilling) test is typically used to diagnose conditions in which intrinsic factor (IF) may be absent, such as pernicious anemia or gastric atrophy.*** *A diagnosis of Intrinsic factor deficiency can be established if radiolabelled cobalamine (Vitamin B12) appears in urine after administration of Intrinsic factor.*

Since cobalamine absorption requires multiple steps including gastric, pancreatic and ileal processes, the Schilling test can also be used to assess the integrity of these other organs.

Dietary vitamin $B_{12}$ is bound in the stomach to an endogenous protein called R protein. Pancreatic enzymes degrade the R protein in the proximal small bowel and lower its affinity for vitamin $B_{12}$ resulting in the rapid transfer of $B_{12}$ to IF; The IF-$B_{12}$ Complex continues to the terminal ileum, where it binds to specific receptors on the surface of the epithelial cells.

***Thus lack of intrinsic factor, lack of sufficient pancreatic enzymes (pancreatic exocrine dysfunction) or presence of terminal Ileal mucosal disease may all result in abnormal vitamin $B_{12}$ excretion.***

**113. Answer is B (In patients with pernicious anemia, the results of the schilling test normalize after oral administration of intrinsic factor):** *Harrison 17th /1878*

***An abnormal Schilling's test that corrects or normalizes after administration of intrinsic factor suggests a diagnosis of Pernicious Anemia (Intrinsic Factor Deficiency).***

***Shilling's test is done to determine the cause of cyanocobalamine deficiency (Vitamin $B_{12}$). Schilling test is abnormal in conditions that affect cobalamine absorption including Pernicious anemia, Chronic Pancreatitis, Bacterial overgrowth syndrome and Ileal dysfunction.***

- *An Abnormal Schilling's test that corrects after administration of Intrinsic Factor indicates Pernicious Anemia*
- *An Abnormal Schilling's test that corrects after administration of Pancreatic Enzymes suggests Exocrine Pancreatic Insufficiency (from Chronic Pancreatitis)*
- *An Abnormal Schilling's test that corrects after administration of five days of antibiotics suggests Bacterial Overgrowth Syndrome*
- *An Abnormal Schilling's test that does not correct after administration of intrinsic factor, pancreatic enzymes and/or antibiotics suggests Ileal mucosal dysfunction*

**114. Answer is A (Small intestinal biopsy):** *Harrisons 16th/1770, 1769; 1879, Harrison 17th/ 1879, 1880 Harrison 18th/p 2468, 2469*

*'Small intestinal mucosal biopsy is essential in the evaluation of a patient with documented steatorrhea or chronic diarrhea (>3 weeks). – Harrisons*

Failure to thrive in the background of recurrent bulky stools and abdominal pain suggests a diagnosis of chronic malabsorption. Although all options provided in the question may be used to support the diagnosis, the most appropriate investigation to make a specific diagnosis is small intestinal biopsy.

**Lesions seen on a small bowel biopsy can be classified into:**

| Specific | | Non Specific |
|---|---|---|
| **Diffuse Specific** | **Patchy Specific** | **Diffuse Non Specific** |
| Whipples Disease | Intestinal lymphoma | Celiac sprue |
| Agammaglobulinemia | Intestinal lymphangiectasia | Tropical sprue |
| Abetalipoproteinemia | Eosinophilic gastroenteritis | Bacterial overgrowth |
| | Amyloids | Folate deficiency |
| | Amyloidosis | Vitamin B12 deficiency |
| | Crohn's disease | Radiation enteritis |
| | Infection by one or more microorganisms | Zollinger-Ellison syndrome |
| | Mastocytosis | Protein-calorie malnutrition |
| | | Drug-induced enteritis |

**115. Answer is C (Appendicitis):** *Harrison 18th/p 2632 Harrisons 17th/2004*

***Appendicitis is not associated with raised amylase levels.***

*Pancreatitis, Ruptured ectopic and salivary gland lesions including blocked salivary duct are all associated with raised amylase levels.*

Pancreatic Disease

1. Pancreatitis
   - A. Acute
   - B. Chronic: ductal obstruction
   - C. Complications of pancreatitis
     - (i) Pancreatic pseudocyst
     - (ii) Pancreatogenous ascites
     - (iii) Pancreatic abscess
     - (iv) Pancreatic necrosis
2. Pancreatic trauma
3. Pancreatic carcinoma

Non pancreatic Disorders

1. Renal insufficiency
2. Salivary gland lesions
   - A. Mumps
   - B. Calculus
   - C. Irradiation sialadenitis
3. "Tumor" hyperamylasemia
   - A. Carcinoma of the lung
   - B. Carcinoma of the esophagus
   - C. Breast carcinoma, ovarian carcinoma
4. Macroamylasemia
5. Burns
6. Diabetic ketoacidosis
7. Pregnancy
8. Renal transplantation
9. Cerebral trauma
10. Drugs morphine

Other Abdominal Disorders

1. Biliary tract disease: cholecystitis, choledocholithiasis
2. Intraabdominal disease
   - A. Perforated or penetrating peptic ulcer
   - B. Intestinal obstruction or infarction
   - C. Ruptured ectopic pregnancy
   - D. Peritonitis
   - E. Aortic aneurysm
   - F. Chronic liver disease
   - G. Postoperative hyperamylasemia

## Celiac Disease

**116. Answer is A (Antiendomysial antibodies):** *Harrisons 16th/1770-1771; Harrison 17th/1881 Harrison 18th/p 2470, 2471*

*Evidence of Malabsorption together with charachteristic histopathological changes on small intestinal biopsy in the form of complete villous atrophy suggests the diagnosis of celiac sprue / disease.*

**Antibody studies are frequently used to identify patients with celiac disease. *'The antiendomysial antibody has 90 to 95% sensitivity and 90 to 95% specificity' in the detection of celiac disease.*** - *Harrisons 16th/1770*

| Celiac disease : Review : *Harrisons 16th/1770-1772* | | |
|---|---|---|
| Malabsorption syndrome of non infectious etiology without systemic features. | | |
| **Etiology** | | |
| **Environmental factors** | **Immunogenic factors** | **Genetic factors** |
| Intolerance to ***gliadin*** a component of gluten, present in wheat, barley, rye and oats | Ig A antibodies are present<br>- ***IgA antiendomysial***<br>- IgA antigliadin<br>- IgA anti tissue tranglutaminase<br>***Antiendomysial antibody has 90-95% Sensitivity and 90-95% Specificity*** | 95% express ***HLA-OQ2 allele***Q |
| **Presentation** | | |
| Malabsorption of multiple nutrients with diarrhea, steatorrhea, weight / loss and consequences of nutrients depletion i.e. anemia and metabolic bone disease | or | Malabsorption of a single nutrient, with iron deficiency anemia or folate deficiency or osteomalacia or edema from protein loss. |
| **Diagnosis** | | |
| 1. **Small intestinal biopsy (duodenal/jejunal)**Q<br>(charachteristic but not diagnostic)Q<br>Absence or reduced height of villi<br>(Flat appearnce)Q<br>• Crypt hyperplasia, villous atrophy (but not mucosal atrophy)Q<br>• Cuboidal appearance of epethelial cells and increased intraepethelial lymphocytes<br>• Increased lymphocytes and plasma cells in lamina propriaQ | | 2. **Antiendomysial antibodies**Q<br>Antiendomysial antibody has 90-95% sensitivity and 90-95% specificity.<br>*Prompt clinical and histopathological response, together with disappearance of Ig Antiendomysial antibodies following institution of a gluten free diet is diagnostic.* |
| **Associated disease**Q | | **Complications** |
| • Dermatitis Herpetoformis Q<br>• Diabetes mellitus type I Q<br>• IgA deficiency | | • Increased incidence of both gastro intestinal and non gastrointestinal neoplasms as well as ***Intestinal lymphomas.***Q |
| **Management** | | |
| Gluten free diet + Glucocorticoids or immunosupressive agents.Q | | |

**117. Answer is C (Defect in chloride channel leading to water reabsorption):** *Refer Cystic Fibrosis Review*

***Thick exocrine secretions in Cystic Fibrosis result from a defect in CFTR Protein which acts as a chloride channel (defect in chloride channel is the primary abnormality).***

*Cystic Fibrosis CF is characterized by a defect in Cystic Fibrosis Transmembrane Regulator (CFTR) gene found on chromosome 7. The CFTR gene codes for the cell membrane transporter protein (CFTR Protein) that normally forms chloride channels in the plasma membrane. Defect in CFTR Protein results in a decrease in chloride permeability across the membrane of epithelial cells of exocrine glands. Since chloride transport across membranes is closely linked to Sodium transport, the defect in chloride channels, leads to an influx of salt and water into the cells resulting in dehydration of the extracellular fluid compartment, an increased chloride concentration in sweat (The basis of diagnostic sweat test) and thickening of exocrine secretions. Virtually all of the clinical manifestations of the disease can be attributed to the thick, tenacious secretions that accumulate in the ducts of exocrine glands*

**118. Answer is B (Anti-endomysial antibody):** *CMDT 2008/530; 09/544; Harrison 18th/p 2470, 2471 Harrison's 17th/1881; 16th/1961, 1986*

*Presence of chronic diarrhea, anemia and elevated liver enzymes is consistent with a diagnosis of Coeliac disease. **Antiendomysial antibodies are highly sensitive and specific for diagnosis of celiac disease and the single best answer of choice amongst the options provided.***

**Approach to diagnosis of Celiac Disease**

| Typical symptoms of Celiac disease | Findings or routine laboratory tests |
|---|---|
| *Chronic Diarrhea*$^{Q}$<br>*Weight's loss*$^{Q}$<br>*Abdominal distension*$^{Q}$<br>*Growth Retardation*$^{Q}$ | • Anemia *(Microcytic or Megaloblastic)*<br>• ***Mild elevation of aminotransferases in upto 40% of patients***<br>• *↑PT /↓Vit A or Vit D*<br>*(Reflect impaired absorption of fat soluble vitamins*<br>• *Low serum $Ca^{++}$ /↑Alk. Phos*<br>*(Reflct impaired $Ca^{++}$ or vit D absorption.* |

Suspect diagnosis of celiac disease and confirm/exclude by performing relevant serological tests

| Serological tests | | |
|---|---|---|
| Two tests with highest diagnostic accuracy are | | |
| *IgA Endomysial Antibody* | : | *≥ 90% sensitivity* |
| *IgA ↓TGA Antibody* | : | *≥ 95% Specificity* |

***Antigliaden antibodies are no longer recommended because of their low sensitivity and specificity.***

**119. Answer is A (Glutin free diet) :** *Harrison 16th / 1772; Harrison 17th/1880, 1881 Harrison 18th/p 2470, 2471*

*Villous atrophy on duodenal biopsy together with positive serological tests for antiendomysial antibodies and IgA anti TTG antibodies suggests the diagnosis of celiac sprue.*

***The mainstay of treatment for celiac sprue is administration of of a glutin free diet.***

*'Removal of all glutin from the diet is essential to therapy'. – CMDT*

*'The most common cause of persistant symptoms in a patient who fulfills all the criteria of diagnosis of celiac sprue is continued intake of gluten'. – Harrison 16th*

**Diagnosis of Celiac Sprue**

**Serological tests** ⟶ **Endoscopic mucosal biopsy** *of distal duodenum or proxi- mal jejunum* ⟶ **Prompt clinical and histo-pathological response follo-wing institution of gluten free diet.**

| **Serological tests** *(CMDT)* | **Endoscopic mucosal biopsy** | **Diagnosis** |
|---|---|---|
| ▪ ***Two serological tests with highest diagnostic accuracy are***<br>1. IgA antiendomysial antibody<br>2. IgA anti – tTG antibody<br>▪ Both tests have a > 90% sensitivity and > 95% specificity. | ▪ Findings are ***characteristic but not specific / diagnostic.***<br>▪ Biopsy of distal duodenum or proximal jejunum is performed.<br>▪ Finding are restricted to mucosa and include :<br>– Loss or blunting of villi / flat villi<br>– Hypertrophy of intestinal crypts<br>– Infiltration of lamina propria will lymphocytes / plasma cells<br>– Cuboidal appearance of epithelial cells and increased intraepithelial lymphocytes. | ▪ **Diagnosis of celiac sprue requires**<br>Presence of characteristic histopathological changes on biopsy together will prompt clinical and hispathological response following institution of gluten free diet.<br>▪ IgA antiendomysial Ab or IgA anti – tTGA Ab should also disappear after a gluten free diet. |
| IgG or IgA antigliadin antibodies are present in 85% of patients with celiac sprue. However their specificity is relatively low (80 – 90%) which limits their usefulness as screening test. | | |
| *Small bowel biopsy is still recommended to confirm diagnosis.* | | |

**120. Answer is A (Antiendomysial antibody):** *Harrison 15th / 1771; Harrison 17th/1881; Harrison 18th/p 2470, 2471 CMDT 2007/615, 616; 09/544; Diagnosis of Celiac disease 'Indian journal of Pediatrics(IJP) vol. 73 Issue 8*

***Antiendomysial antibodies have a high sensitivity and specificity for diagnosis of celiac sprue and show best performance for detection of celiac sprue.***

| Antiendomysial antibody > Anti tissue transglutaminase antibody > Antireticular antibody> Antigliadin antibody | | | |
|---|---|---|---|
| **Antigliadin (IJP) Antibodies (AGN)**<br>• First immunological assay to be tested were antigliadin antibodies.<br>• The variability and lower accuracy make them *unsuitable for diagnostic and screening purposes*<br>• Antigliadin assays have been replaced by more specific and sensitive tests using other antibodies | **Anti reticulin IJP Antibodies (ARA)**<br>• Second antibody identified in literature was the antireticulin antibodies.<br>• There are atleast 5 types of antireticulin antibodies but only one type is associated with celiac disease.<br>• These antibodies are *not very sensitive and are not used in routine practice.* | **Antiendomysial Antibiotics (Anti EMA)**<br>• Antiendomysial antibodies have ***high sensitivity and specificity*** for the diagnosis of celiac disease.<br>• These antibodies are directed against endomysium or 'Intermyofibril substance' of smooth muscle.<br>• The antigen recognized by these antibodies is 'tissue transglutaminase'. | **Anti tissue transglutaminase antibody (Anti-tTGA)**<br>• Major breakthrough for serological diagnosis of celiac disease.<br>• Antitissue transglutaminase antibodies (Anti-tTGA ) are ***also highly sensitive and specific but performance of anti EMA is superior to Anti-tTGA*** |

**Anti EMA and Anti-tTGA**

*While the performance of Anti-EMA is superior to Anti – tTGA, the discovery of Anti-tTGA is seen as a major breakthrough. Why ?*

| Anti-EMA | Anti – tTGA |
|---|---|
| • Anti EMA are species specific reacting only with gastrointestinal tract of primates. They are identified using indirect immunoflorescence on frozen section of monkey esophagus.<br>• Interpretation of immunoflorescence assay is ***operator dependent and more liable to errors in less experienced hands.*** | • ELISA based assays are available for detection of anti – tTGA.<br>• Initial tests used guinea pig antigen but now human recombinant tTGA are available.<br>• ELISA based detection is ***simpler and more accessible diagnostic test*** |

Recommended reading : Article on 'Diagnosis of celiac disease' by AIIMS faculty published in 'Indian Journal of Pediatric' 2006; volume 73 issue 8 (Available on internet)

*A recent systemic review of the diagnostic performance of the serological tests reported in studies from 1996 to 2003 showed that in children:*

| Parameter | Anti-EMA | Anti-tTGA (Human Recombinant) |
|---|---|---|
| Specificity | 100% (pooled monkey esophagus and human umbilical cord) | 95 – 95% (pooled + TG guinea pig and human recombinant) |
| Sensitivity | 96% (monkey esophagus) | 96% (human recombinant) |

***Anti-tTGA is highly sensitive and specific but performance of anti EMA is superior to Anti-tTGA***

**121. Answer is B (Increase in thickness of mucosa):** *Pathologic basis of Disease by Robbins 5th/797 Harrison's 16th/1770-71; 17th/1881 Harrison 18th/p 2470*

***The overall mucosal thickness remains the same*** *- Robbins*

***Pathologic morphology of celiac disease:***

The mucosa appears flat or scalloped or may be visually normal. Biopsy specimens demonstrate a diffuse enteritis, with the following features.

| The villi | The surface epithelium | The crypts | The lamina propria |
|---|---|---|---|
| show marked atrophy or total loss. | shows vacuolar degeneration, loss of the microvillus brush border, and an increased number of intraepithelial lymphocytes. | exhibit increased mitotic activity and are elongated, hyperplastic and tortuous, so the overall mucosal thickness remains the same. | has an overall increase in plasma cells, lymphocytes, macrophages, eosinophils and mast cells. |

*All these* ***structural changes are more marked in the proximal small intestine*** $^{Q}$ *than in the distal because it is the duodenum and proximal jejunum that are exposed to the highest concentration of the dietary gluten.*

**122. Answer is C and E (Mucosal atrophy & Presence of Giardia lambia):** *Harrison 18th/p 2471 Harrison's 17th/1881*

***Mucosal atrophy and presence of Giardia Lambia are not seen in biopsy from celiac disease.***

| Small Intestinal Biopsy (duodenal /jejunal) in Celiac disease (Characteristic but not diagnostic$^{Q}$) |
|---|
| • Absence or reduced height of villi (Flat appearance)$^{Q}$ |
| • Crypt hyperplasia, villous atrophy (but not mucosal atrophy)$^{Q}$ |
| • Cuboidal appearance of epithelial cells and increased intraepithelial lymphocytes |
| • Increased lymphocytes and plasma cells in lamina propria$^{Q}$ |

**123. Answer is A (Dermatitis Herpetiformis):** *Harrisons 17th/1881 CMDT 2008/ 529, 530; 09/544*

***Celiac disease is associated with Dermatitis Herpetiformis***

*'Dermatitis Herpetiformis is regarded as cutaneous variant of celiac disease. Almost all patients with dermatitis Herpetiformis have evidence of celiac disease on intestinal biopsy' – CMD*

| Associations of Celiac Disease (CMDT & Harrisons) |
|---|
| • ***Dermatitis Herpetiformis*** |
| • Other autoimmune disease including: *(CMDT)* |
| - *Addison's disease* |
| - *Grave's disease* |
| - *Diabetes mellitus- Type I (Harrisons)* |
| - *Myaesthenia Gravis* |
| - *Slogren syndrome* |
| - *Atrophic Gastritis* |
| - *Pancreatic insufficiency* |
| • IgA deficiency *(Harrisons)* |
| • Lymphomas *(Harrisons)* |

**Note**

**Celiac disease is associated with an increased risk of cancer including Lymphomas (NHL, Intestinal T cell Lymphoma)**

*The possibility of Lymphoma must be considered whenever a patient with celiac sprue previously doing well on a gluten free diet is no longer responsive to gluten free diet' - Harrisons*

**124. Answer is E (All of the above):** *Harrisons 17th/1881, 1882 CMDT 2008/530*

***Celiac disease may be associated with Dermatitis Herpetiformis and other autoimmune diseases including type I D.M and Atrophic gastritis. It is also associated with increased risk of cancer including Lymphomas.***

**125. Answer is A and B (Intestinal biopsy and Unequivocal response to gluten restriction):** *Harrison 18th/p 2470, 2471 Harrisons 17th/1881*

***'The diagnosis of celiac disease requires the presence of characteristic histological changes on small intestinal biopsy together with a prompt and clinical and histological response (unequivocal response) following the institution of gluten free diet' – Harrisons 17th/1881***

**126. Answer is A (Rice):** *Harrisons 16th/1772*

***Rice is Gluten free and should be used in place of wheat flour in patients with Gluten sensitivity or celiac sprue***

| Gluten Containing Grains | Gluten Free Grains |
|---|---|
| • *Wheat* | • *Rice* |
| • *Rye* | • *Corn* |
| • *Oat* | • *Millet* |
| • *Barley* | • *Topioca* |
| • *Spelt* | |

**127. Answer is A and D (Rice and Corn):** *Refer previous question*

***Rice and Corn are Gluten free grains that can be safely consumed in patients with gluten hypersensitivity***

**128. Answer is D (Vitamin $B_{12}$):** *Celiac Disease for Dummies' by Blumer & Crowe (John Wiley & Sons 2010*

***Vitamin $B_{12}$ deficiency may be seen in celiac disease but the deficiency of this vitamin is uncommon in patients with celiac disease. Vitamin $B_{12}$ is the single best Answer amongst the option provided.***

*'Vitamin $B_{12}$ is absorbed from the body in the end part of small intestine (terminal ileum). Because this part of the bowel is seldom damaged - by celiac disease, Vitamin B12 deficiency is not common in this condition'- Celiac Disease for Dummies*
*'Vitamin D Deficiency is particularly frequent in people with celiac disease' - Celiac Disease for Dummies*
*'Folic acid Deficiency is fairly common in people with celiac disease' - Celiac Disease for Dummies*
*'Vitamin A Deficiency is common in people with celiac disease - Celiac Disease for Dummies*

**Vitamin Deficiency in Patients with Celiac disease**

| Fat Soluble Vitamins | Other Vitamins |
|---|---|
| *Vitamin A (common)* | • *Folic acid (common)* |
| *Vitamin D (common)* | • *Vitamin $B_{12}$ (uncommon)* |
| *Vitamin E (uncommon)* | |
| *Vitamin K (uncommon)* | |

## Whipple's Disease

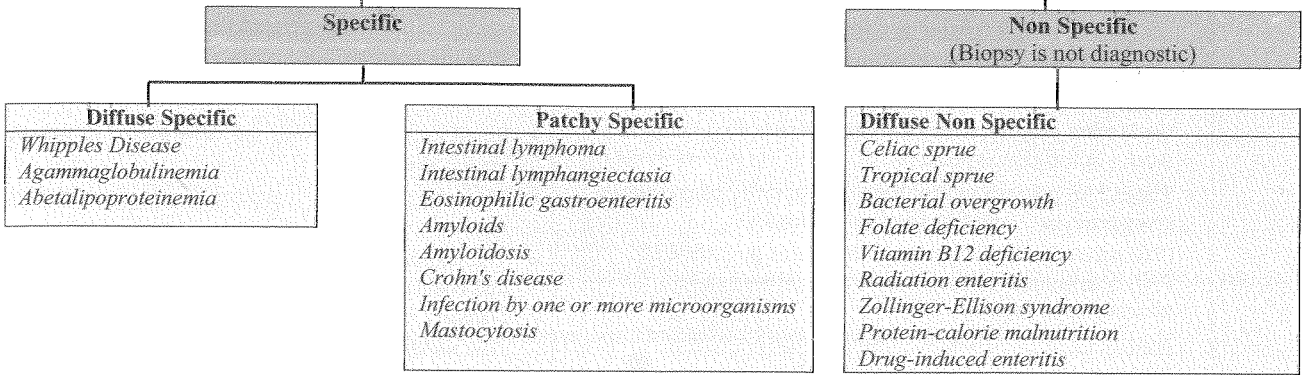
**129. Answer is C (Whipple's Disease):** *Harrison 18th/2470; Harrison's 17th/1880; Harrison's 16th/1769, 1770*

***An intestinal biopsy is diagnostic/specific for malabsorption due to Whipple's disease.***

**Three most commonly asked forms of Malabsorption Syndromes :**

| *Whipple's Disease* | *Tropical Sprue* | *Coeliac Disease* |
|---|---|---|
| Malabsorption syndrome with systemic features with infectious etiology | Malabsorption syndrome of infectious etiology without systemic features | Malabsorption syndrome of non infectious etiology without systemic features |
| **Etiology** | **Etiology** | **Etiology** |
| Gram negative actinomycete Tropheryma whippelii | Caused by some strains of E.coli | Caused by intolerance to 'gliadin' gluten a protein found in wheat rye, barley. |
| **Biopsy** | **Biopsy** | **Biopsy** |
| **Biopsy is Abnormal and specific/diagnostic** | **Biopsy is abnormal but not specific/diagnostic** | **Biopsy is abnormal but not specific/diagnostic** |
| Lamina Propria is infiltrated with macrophages containing PAS positive glycoproteins and rod shaped bacilli<br>Dilated lymphatics | Shortened, thickened villi increased crypt depth infiltration by mononuclear cells | Blunting and flattening surface with villi either absent or broad and short<br>Crypts are elongated<br>Dense infiltration of inflammatory cells in lamina propria |
| **Clinical features** | **Clinical features** | **Clinical features** |
| Features of malabsorption<br>+ Array of systemic features | Features of malabsorption | Features of malabsorption |
| **Management** | **Management** | **Management** |
| Etiology is infectious so treatment is with Antibiotics<br>Trimethoprim+sufamethoxocate | Etiology is infectious so treatment is with antibiotics (Sulfonamide/ Tetracycline) | Etiology is not infectious but immune<br>Glutin free diet (no antibiotics) + Glucocorticoids or immunosuppressive agents |

**Lesions seen on a small bowel biopsy**




**130. Answer is A (Whipple's Disease):** *Robbins 5th/799; 7th/843, 844; Harrison 16th/1774, 1772, 1770; 17th/1884, 1879 Harrison 18th/p 2469, 2474*

***The hallmark of Whipple's disease is a small intestinal mucosa laden with distended macrophages in the lamina propria- the macrophages contain periodic acid-schiff (PAS) positive granules and rod shaped bacilli by electron microscopy.***

**Three most commonly asked forms of Malabsorption Syndromes :**

| ***Whipple's Disease*** | ***Tropical Sprue*** | ***Coeliac Disease*** |
|---|---|---|
| Malabsorption syndriome with systemic features with infectious etiology | Malabsorption syndrome of infectious etiology without systemic features | Malabsorption syndrome of non infectious etiology without systemic features |
| **Etiology** | **Etiology** | **Etiology** |
| Gram negative actinomycete♀ Tropheryma whippelii | Caused by some strains of E.coli | Caused by intolerance to 'gliadin' gluten a protein found in wheat rye, barley♀. |
| **Biopsy** | **Biopsy** | **Biopsy** |
| ***Diagnostic*** | ***Abnormal but Not Diagnostic*** | ***Abnormal / Characteristic but Not Diagnostic*** |
| Lamina Propria is infiltrate with of macrophages containing PAS positive glycoproteins and rod shaped bacilli<br>Dilated lymphatic | Shortened, thickened villi increased crypt depth infiltration by mononuclear cells | Blunting and flattening surface with villi either absent or broad and short<br>Crypts are elongated<br>Dense infiltration of inflammatory cells in lamina propria inflammatory |
| **Clinical features** | **Clinical features** | **Clinical features** |
| Features of malabsorption + Array of systemic features | Features of malabsorption | Features of malabsorption |
| **Management** | **Management** | **Management** |
| Etiology is infectious so treatment is with Antibiotics Trimethoprim+sufamethoxocate | Etiology is infectious so treatment is with antibiotics Antibiotic (Sulfonamide/ Tetracycline) | Etiology is not infectious but immune Glutin free diet (no antibiotics) + Glucocorticoids or immunosuppressive agents |

**131. Answer is B (Marked increase in the number of intraepethelial lymphocytes):** *Robbins 7th/844*
*Samter's Immunologic Disease by Austen & Samter 2nd/ 704; Sternberg's Diagnostic Surgical Pathology 4th /1481*

The intraepethelial lymphocytes are usually, either decreased in number or normal.
Marked increase in the number of intraepethelial lymhocytes is not seen and this is the single best answer of exclusion.

**The Hallmark of Whipple's disease is a** small intestinal mucosa laden with macrophages. **Accompanying changes include** lymphatic dilatation **suggesting lymphatic blockage. The lymphatic blockage is believed to be responsible for** lipid deposition **in the villi** – *Robbins*

**Histopathological findings in Whipple's disease**

| Characterisitc findings / Specific finding (Hallmark of disease) | Associated findings |
|---|---|
| • Small intestinal mucosa laden with ***foamy macrophages in the lamina propria***, which are characteristically, Periodic – Acid – Schiff (PAS) positive.<br>• These PAS positive macrophages (monocytes) also *contain gram positive – acid fast bacillus T. whipleii*[Q].<br>(The substance in macrophages that stains positive with PAS is thought to be remnants of the cell wall of phagocytosed bacilli)<br>Note :<br>*PAS positive macrophages are not pathognomic for Whipple's disease. They have also been isolated in other diseases eg. Mycobacterium Avium Intercellulare & Mycobacterium Tuberculosis.* | • Villi may be thickenned, widened or blunted<br>• Small intestinal mucosal and ***submucosal lymphatic vessels are dilated***<br>• Lipid droplets / Lipid vacuoles / ***Lipid deposition may be seen***<br>• The number of lamina propria plasma cells, ***lymphocytes*** and eosinophills ***are decreased*** *(Samter's Immunologic Diseases by Austen and Samter 2nd /704)*<br>*'The number of intraepethelial lymphocytes is not increased'*<br>*(Sternberg's Diagnostic Surgical Pathology 4th/1481)* |

**Disease that can be Diagnosed by Small-Intestinal Mucosal Biopsies**

| Lesions | Pathologic Findings |
|---|---|
| Diffuse, specific | |
| • *Whipple's disease* | Lamina propria contains macrophages containing PAS + material |
| • *Agammaglobulinemia* | No plasma cells; either normal or absent villi ("flat mucosa") |
| • Abetalipoproteinemia | Normal villi; epithelial cells vacuolated with fat postprandially |
| Patchy, specific | |
| • *Intestinal lymphoma* | Malignant cells in lamina propria and submucosa |
| • *Intestinal lymphangiectasia* | Dilated lymphatics; clubbed villi |
| • *Eosinophilic gastroenteritis* | Eosinophil infiltration of lamina propria and mucosa |
| • *Amyloidosis* | Amyloid deposits |
| • *Crohn's disease* | Noncaseating granulomas |
| • *Infection by one or more microorganisms* | Specific organisms |
| • *Mastocytosis* | Mast cell infiltration of lamina propria |
| Diffuse, nonspecific | |
| • *Celiac sprue* | Short or absent villi; mononuclear infiltrate; epithelial cell damage; hypertrophy of crypts |
| • *Tropical sprue* | Similar to celiac sprue |
| • *Bacterial overgrowth* | Patchy damage to villi; lymphocyte |
| • *Folate deficiency* | Short villi; decreased mitosis in crypts; megalocytosis |
| • *Vitamin B12 deficiency* | Similar to folate deficiency |
| • *Radiation enteritis* | Similar to folate deficiency |
| • *Zollinger – Ellison syndrome* | Mucosal ulceration and erosion from acid |
| • *Protein –calorie malnutrition* | Villous atrophy; secondary bacterial overgrowth |
| • *Drug-induced enteritis* | Variable histology |

**132. Answer is D (Dementia) :** *Harrison 14th / 1627, 15th/1667, 16th/1774; 17th/ 1884; Harrison 18th/p 2474 CMDT 2003 / 587; 09/546*

*CNS manifestations in Whipples disease include dementia (presenting as confusion in memory loss) along with focal features such as Seizures.* ***Non specific symptoms like Confusion and Memory loss (Dementia) in all likelihood, should be more common a presentation than seizures.***

**Whipple's disease** is a rare multisystemic illness caused by infection with the bacillus *'Tropheryma Whippelii'* ?

- *Essential of Diagnosis include :*
  a. Malabsorption ?
  b. Multisystemic involvement along with Fever, Lymphadenopathy and Arthralgias ?
  c. Duodenal Biopsy with PAS positive macrophages ? showing characteristic bacillus (with large cytoplasmic granules)?
- *CNS invovement is seen in about 10%* of patients. Manifestations include
  - ***Dementia*** ? (confusion and memory loss)
  - Seizures, Coma, Myoclonus ?
- *Cranial N. findings* include Nystagmus and Ophthalmoplegia ?

  Non specific symptoms like Confusion and Memory loss (Dementia) in all likelihood, should be more common a presentation than seizures.

  ***Ophthalmopegia is due to cranial nerve involvement and not supra-nuclear in type.***

**133. Answer is D (Abetalipoprotenemia):** *Harrison 18th/ ; Manson's Tropical Diseases: Expert Consult (Elsevier Health Sciences, 2013) / 672; The Washington Manual of Surgical Pathology (Lippincott Williams & Wilkins, 2008)/ 186*

***Abetalipoproteinemia is typically associated with normal villus architecture and no inflammatory reaction.*** Features of lipid accumulation within enterocytes (vacuolated epithelial cells) is diagnostic and specific.

Crohn's Disease and Whipple's disease are typically associated with inflammation.
Giardiasis also does not induce significant villous architectural change or an inflammatory response. Majority of patients with Giardiasis have none or relatively mild abnormalities of villous architecture and no or minimal inflammation. However the full spectrum of abnormalities ranging from normal to subtotal villous atrophy has been described in human giardiasis. Patients with symptomatic giardiasis may have normal villous architecture with no mucosal inflammation and if abetalipoproteinemia was not provided amongst the options, Giardiasis should have been the single best answer of choice. ***Patients with symptomatic giardiasis may have normal villous architecture with no mucosal inflammation and if abetalipoproteinemia was not provided amongst the options, Giardiasis should have been the single best answer of choice***

**134. Answer is A (Giardiasis):** *The Washington Manual of Surgical Pathology (Lippincott Williams & Wilkins, 2008)/ 186*

***Giardiasis also does not induce significant villous architectural change or an inflammatory response. Majority of patients with Giardiasis have none or relatively mild abnormalities of villous architecture and no or minimal inflammation.***

| However the full spectrum of abnormalities ranging from normal to subtotal villous atrophy has been described in human giardiasis. |
|---|

**135. Answer is D (Giardiasis):** *Harrison 16th/1249, CMDT 6th/1479 (Repeat)*

***Giardia** should be considered in most cases of diarrhoea, especially when it is prolonged and associated with marked weight loss. **Syndromes** include, acute diarrhoea, chronic diarrhoea and **malabsorption.**- CMDT*
*Disease manifestation of **giardiasis** range from asymptomatic carriage to fulminant diarrhoea and **malabsorption.'***
*- Harrison*

## Short Bowel Syndrome

**136. Answer is B (Hypogastrinemia):** *Harrison 15th/1676; Harrison 16th/11773; Harrison 17th/1882, 1883 Harrison 18th/p 2472, 2473*
***Short bowel syndrome is characterized by increased gastrin levels (hypergastrinemia) due to reduced small intestinal catabolism of gastrin** – Harrison's*

**Short bowel syndrome** *(Myriad of clinical problems that follow resection of warying length of small intestine)*

**Causes:**

1. *Mesentric vascular disease: mesenteric ischaemia?*
2. *Primary mucosal and submucosal disease – Crohn's disease?*
3. *Operations without preexisting small intestinal disease – jejunoilial bypass for obesity?*

**Manifestation resulting from resection of varying length of small intestine**

| Diarrhea and Steatorrhea [Q] | ↑ed Renal calcium oxalate calculi | ↑ed Cholesterol gall stones [Q] | Gastric hypersecretion of acid [Q] |
|---|---|---|---|
| Multiple factors contribute to diarrhea and steatorrhea such as:<br>• Absence of intestinal mucosa required for absorption of lipid and fluid and electrolytes<br>• Stimulation of colonic fluid and electrolyte secretion by increased bile acids that enter colon<br>• Decreased intestinal transit and bacterial overgrowth from absence of ilio caecal valve<br>• Reduced pH in duodenum from gastric acid hypersecretion. | • There occurs increased absorption of oxalates by large intestine in patients with a small intestinal resection with intact colon<br>• Hyperoxaluria and renal calcium oxalate crystals form<br>**Treatment:**<br>• Dietry restriction of oxalate containing feed (spinach, tea)<br>• Cholestyramine an anion binding resin and calcium | Due to a decrease in the bile acid pool size and resulting super saturation of cholesteral in gall-bladder bile. | Related to reduced hormonal inhibition of acid secretion or increased gastrin levels due to reduced small intestine catabolism of gastrin. |

**137. Answer is B (Iron deficiency anaemia):** *Harrison 17th/1882, 1883 Harrison 18th/p 2472, 2473*

***Iron is primarily absorbed in duodenum therefore ileal resection will not cause iron deficiency anaemia.***
*All other options are true and explained in the previous question.*

**138. Answer is A (Vitamin B12):** *'Complications in Surgery' (Lippincott Williams) 2nd (2011)/469; Sleisenger and Fordtran's Gastrointestinal Diseases 8th/2258, 2264*

***Cyanocobalamine (Vitamin B12) deficiency is the most common deficiency in patients with short bowel syndrome associated with loss of ileum (ileal resection) since vitamin B12 is absorbed only in the ileum.***

*'Cyanocobalamine (Vitamin B12) is the most common deficiency and occurs predictably after resection of 50-60 cm of the terminal ileum'. – 'Complications in Surgery' (Lippincott Williams) 2nd (2011)/469*

*'Vitamin B12 and Bile acids are absorbed only in the ileum. Loss of ileum results in malabsorption of bile acids and vitamin B12 and consequent vitamin B12 deficiency'– 'Sleisenger and Fordtran's Gastrointestinal Diseases' 8th/2258, 2264*

*Vitamin Deficiencies in Short Bowel Syndrome*

**Short Bowel Syndrome with Extensive Jejunal Resection**

- This is associated primarily with deficiency of fat soluble vitamins (A, D, E, K)
- *The most common fat-soluble vitamins that are deficienct are vitamin A and D and to a lesser extent vitamin E followed by vitamin K.*

Vitamin A, D > Vitamin E >> Vitamin K

**Deficiency of vitamin K is uncommon as vitamin K is synthesized by colonic bacteria**

- 60% of vitamin K is synthesized by colonic bacteria
- 40% of vitamin K is received by dietary intake
- *Deficiency of vitamin K is therefore uncommon in patients with short bowel syndrome who have an intact colon.*
- *Deficiency of vitamin K is however common in those patients with short bowel syndrome who do not have a residual colon.*

**Short Bowel Syndrome with Extensive ileal resection**

- This is associated primarily with deficiency of vitamin B12 since vitamin B12 is only absorbed in the terminal ileum.
- Fat soluble vitamin deficiencies may also occur due to fat malabsorption from decrease in concentration of bile acids / salts.

(Bile acids are absorbed only from the ileum)

Vitamin B12 > Fat solubleVitamin

*The ileum has the capacity to adapt and compensate for jejunal resection. The jejunum does not have the capacity to adapt and compensate for ileal resection (as the terminal ileum has the exclusive capacity to reabsorb bile salts &vit $B_{12}$)*

**139. Answer is A (Vitamin B12):** *Refer previous question; 'Clinical Nutrition in Gastrointestinal Disease' by Buchman (2006)/362*

***Cyanocobalamine (Vitamin B12) deficiency is the most common deficiency in patients with short bowel syndrome associated with loss of ileum (ileal resection) since vitamin B12 is absorbed only in the ileum***

*Short Bowel Syndrome may be associated with deficiency of fat-soluble vitamins (Vitamin A, D, E and K) and water soluble Vitamin B12 (when ileum is resected / non functional).*

***The most common deficiency is determined essentially by the specific segment of the small intestine (jejunum or ileum) that is resected / non functional.***

*Since the question does not specify the specific segment of the small intestine contributing to the short bowel syndrome, the single best answer has to be selected by a method of exclusion.*

**Vitamin B12 is the single best answer amongst the options provided** (*since none of the commonly deficient fat soluble vitamins (A, D or E) have been provided amongst the options and deficiency of Fat soluble Vitamin K is uncommon in Short Bowel Syndrome)*

**Deficiency of fat-soluble vitamin K is uncommon in short bowel syndrome***since 60% of the vitamin K is synthesized in the colon*

**Deficiency of water-soluble vitamins Biotin and Thiamine is uncommon in short bowel syndrome** *since thay are primarily absorbed in the duodenum and/or proximal jejunum.*

***Short Bowel Syndrome is primarily associated with deficiency of fat-soluble vitamin (A, D and E) and water-soluble vitamin B12 (since this water soluble vitamin is absorbed only in the ileum)***

## Intestinal Angina

**140. Answer is B (Postprandial Abdominal Pain, Weight loss and Chronic mesenteric vessel occlusion) :** *Harrison 16th/1799; 17th/1911*

***Chronic intestinal ischemia*** *presents with* ***intSestinal angina*** *or abdominal pain associated with need for increased blood flow to the intestine.*

***Patients report abdominal pain cramping and pain following ingestion of meal (postprandial abdominal pain Weight loss and chronic diarrhea are also noted*** *- Harrison 16th / 1799*

**What is Intestinal Angina : Journal of Emergency Medicine : Review Article.**

- Intestinal angina refers to the clinical syndrome seen in association with ***Chronic Mesenteric Ischaemia.***
- It is characterized by reduced mesenteric blood flow that interferes with physiological function but does not cause infarction.
- Mesentric angina is the result of intestinal hypoperfusion through two of the three major vessels supplying the small intestine.
  - Superior Mesentric Artery
  - Celiac artery
  - Inferior Mesentric Artery

**Presentation**

- Post Prandial Abdominal Pain : Abdominal pain that starts about 30 minutes after eating and lasts for one to two hours.
- Fear of eating and weight loss : Once the patient realizes the relationship between eating and pain.
- Diarrhea, Nausea, Vomiting

**Diagnosis**

- *Gold standard for confirmation of mesenteric arterial occlusion (chronic mesenteric ischaemia) is Angiography - Harrison*

  (*Note that Gold standard for diagnosis of acute mesenteric ischaemia is Laparotomy*$^{Q}$*. Surgical exploration should not be delayed*).

# Inflammatory Bowel Disease

## Ulcerative Colitis

**141. Answer is A (Ulcerative Colitis):** *Harrison 18th/p 2486 Harrison's 17th/1892*

***Presence of mucus and blood in stool along with positive ANCA antibodies suggests a diagnosis of ulcerative colitis***

**Different Clinical, Endoscopic and Radiographic Features**

| | Ulcerative Colitis | Crohn's Disease |
|---|---|---|
| **Clinical** | | |
| ***Gross blood in stool*** | ***Yes*** | ***Occasionally*** |
| ***Mucus*** | ***Yes*** | ***Occasionally*** |
| Systemic symptoms | Occasionally | Frequently |
| Pain | Occasionally | Frequently |
| Abdominal mass | Rarely | Yes |
| Significant perineal disease | No | Frequently |
| Fistulas | No | Yes |
| Small-intestinal obstruction | No | Frequently |
| Colonic obstruction | Rarely | Frequently |
| Response to antibiotics | No | Yes |
| Recurrence after surgery | No | Yes |
| ***ANCA-positive*** | ***Frequently*** | ***Rarely*** |
| ASCA –positive | Rarely | Frequently |
| **Endoscopic** | | |
| Rectal sparing | Rarely | Frequently |
| Continuous disease | Yes | Occasionally |
| Cobblestoning | No | Yes |
| Granuloma on biopsy | No | Occasionally |
| **Radiographic** | | |
| Small bowel significantly abnormal | No | Yes |
| Abnormal terminal ileum | Occasionally | Yes |
| Segmental colitis | No | Yes |
| Asymmetric colitis | No | Yes |
| Stricture | Occasionally | Frequently |
| **Epidemiology of IBD** | | |
| Age of onset | 15-30 and 60-80 | 15-30 & 60-80 |
| Male : Female ratio | 1:1 | ≈1.5 : 1 |
| Smoking | May prevent disease | May cause disease |
| Oral contraceptives | No increased risk | Odds ratio 1.4 |
| Appendectomy | Protective | Not protective |
| Monozygotic twins | 6% concordance | 58% concordance |
| Dizygotic twins | 0% concordance | 4% concordance |

**142. Answer is B > A (Ulcerative colitis > Crohn's disease):** *Robbins 7th/848, 850, Harsh mohan 5th/ 582, 584*

*Chronic diarrhea, crypt abscess and crypt ulcers may be seen in both forms of inflammatory bowel disease i.e, Ulcerative colitis and Crohn's disease.* However ***cryptitis and crypt abscesses represent the charachteristic microscopic features in Ulcerative Colitis. Ulcerative colitis is therefore the single best answer of exclusion.***

**According to Harrison**

***The characteristic microscopic findings in Ulcerative colitis are crypt distortion,cryptitis and crypt abscesses*** *(*Harrisons 16th/1778, Fig 276-2*)*

Note

Crypt Abscesses are not specific for Ulcerative colitis and may be seen in CD or any other active inflammatory colitis.

*The characteristic microscopic findings in Crohn's disease are non-casseating granulomas in* all layers of the bowel wall from mucosa to serosa

*However*

Aphthoid ulcers and focal ***crypt abscesses*** *are also seen (early lesions) in Crohn's disease (Harrisons 16th/1779)*

*Pathological examination of the bowel wall is Crohn's disease is more likely to reveal Non casseating granulomas in association with these crypt abscesses while in the case of Ulcerative colitis, crypt abscesses and cryptitis may be the only pathological finding. As the pathological examination does not mention the presence of Non casseating granulomas we may presume that these were not found during the pathological examination of specimen.* ***In the absence of non casseating granulomas, the presence of cryptitis and crypt abscesses favours a diagnosis of ulcerative colitis.***

**DISTINGUISHING FEATURES OF CROHN'S DISEASE AND ULCERATIVE COLITIS :**

| FEATURE | CROHN'S DISEASE | ULCERATIVE COLITIS |
|---|---|---|
| **A. Macroscopic features** | | |
| *1. Distribution* | Segmental with ***skip areas*** Q | Continuous *without skip areas* Q |
| *2. Location* | Commonly terminal ileum and /or ascending colon | Commonly rectum sigmoid colon and extending upwards |
| *3. Extent* | Usually involves the entire thickness of the affected segment of bowel wall | Usually superficial, confined to mucosal layers |
| *4. Ulcers* | Serpiginous ulcers, that may develop into deep *Fissures* Q | Superficial mucosal ulcers without fissures |
| *5. Pseudopolyps* | Rarely seen | *Commonly present* Q |
| *6. Fibrosis* | Common | Rare |
| *7. Shortening* | Due to fibrosis | Due to contraction of muscularis |
| **B. Microscopic features** | | |
| *1. Depth of inflammation* | *Typically transmural* Q | *Mucosal* Q and Submucosal |
| *2. Type of inflammation* | *Non-caseating granulomas* Q and infiltrate of mononuclear cells (lymphocytes, plasma cells and macrophages) (Crypt abscess may also be seen) | *Crypt abscess* and non-specific acute and chronic inflammatory cells (lymphocytes, plasma cells neutrophils, eosinophils, mast cells) |
| *3. Mucosa* | Patchy ulceration | Hemorrhagic mucosa with ulceration |
| *4. Submucosa* | Widened due to edema and lymphoid aggregates | Normal or reduced in width |
| *5. Muscularis* | Infiltrated by inflammatory cells | Usually spared, except in cases of ***Toxic Megacolon*** Q |
| *6. Fibrosis* | Present | Usually absent |
| **C. Complications** | | |
| *1. Fistula formation* | Internal and external fistulae in 10% cases | *Extremely rare* Q |
| *2. Malignant changes* | Less common but present | May occur in disease of more than 10 years duration (*more common* Q) |
| *3. Fibrous strictures* | *Common* Q | *Never* Q |
| *4. Toxic Megacolon* | -- | Risk present Q |
| 5. Named Features | *Hose pipe appearance* Q *Cobble-Stone appearance* Q | *Garden hose appearance* Q *Pseudopolyps* Q |

**143. Answer is A (Ulcerative Colitis) :** *Harsh Mohan 4th / 543*

***Toxic megacolon is an important complication of ulcerative colitis.***

**144. Answer is B (Ulcerative colitis) :** *Refer previous question*

Colonic involvement with ulcerative colitis is characterised by extensive, broad based ulceration of the mucosa in the distal colon or throughout its length. ***Pseudopolyps are created by bulging upwards of isolated islands of regenerating mucosa.***

**145. Answer is B (Ulcerative colitis):** *Robbins 7th/848, 850; Harsh Mohan 5th/582, 584*

***Pseudopolyps are typically seen in Ulcerative colitis.***

**DISTINGUISHING FEATURES OF CROHN'S DISEASE AND ULCERATIVE COLITIS:**

| FEATURE | CROHN'S DISEASE | ULCERATIVE COLITIS |
|---|---|---|
| ***Pseudopolyps*** | **Rarely seen** | ***Commonly present*** Q |

**146. Answer is B (Rectum)**

***The most common site of involvement in Ulcerative Colitis is the Rectum.***

**Ulcerative Colitis (Involvement is limited to the Colon)**

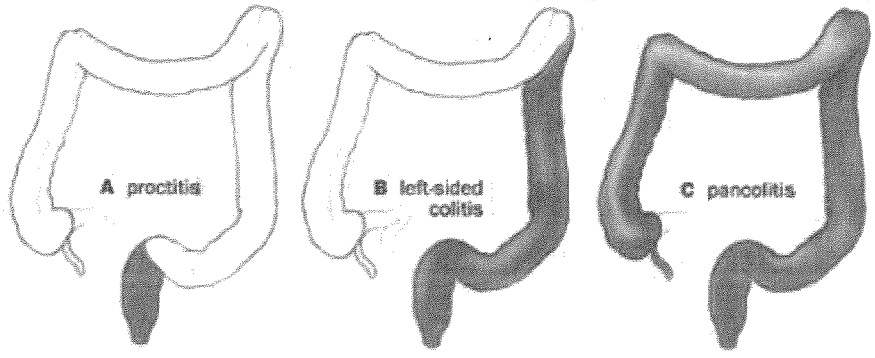
Ulcerative colitis typically starts in the Rectum and may progress with *continuous lesions* (no skip lesions) in a retrograde manner to involve the entire colon (Pancolitis)

***Since the Rectum is almost always involved in UC, the Rectum is the single most common site***

***Ulcerative Colitis by definition is a disease limited to the colon that does not involve the ileum. Terminal Ileum may however be involved in Ulcerative colitis by Backwash ilitis***

**Left Sided Colonic Predominance is typical**

The extent of disease is variable and may involve only the rectum (ulcerative proctitis), the left side of the colon to the splenic flexure(left sided colitis) or the entire colon (pancolitis).




**147. Answer is A (Ulcerative Colitis)**

*Involvement of the terminal Ileum in Ulcerative Colitis is termed as Backwash Ileitis*

*The term 'Backwash Ileitis' was originally used to describe an abnormal appearance of the terminal ileum observed radiologically or endoscopically in patients with ulcerative pancolitis. The term derives from the original contention that the ileitis resulted as a reaction to 'the reflux of colonic contents into the terminal ileum'. Currently such ileitis is UC is considered to be primarily ileal mucosal inflammation.*

**Ileitis in Ulcerative Colitis: Backwash Ileitis**

*Ulcerative colitis is classically defined as an inflammatory process of the colon with sparing of the ileum. Ileal inflammation has however been described in a subset of patients with ulcerative colitis. It has been presumed that the mechanism of distal ileal inflammation in ulcerative colitis is pancolitic associated reflux of colonic contents into the ileum through an incompetent ileocecal valve with subsequent ileal inflammation and hence termed as "backwash" ileitis. In contrast to the more extensive ileal involvement of Crohn's disease, ileal inflammation in ulcerative colitis is generally limited to only a few centimeters proximal to the ileocecal valve.*

**148. Answer is D (5-Aminosalicyclic acid):** *Harrison 18th/2489; Harrison 17th/1815; Read text below*

***'The mainstay of therapy for inflammatory bowel disease remains 5 Aminosalicyclic derrivativs. – CMDT***

**5 Aminosalicyclic acid:**

It is used in active treatment of ulcerative colitis and Crohn's disease and during disease inactivity in order to maintain remission.

| Commonly used formulations of 5 ASA are : |
|---|
| Sulfasalazine |
| Oral mesolamine agents |
| Azo compounds : Balsalazide, Olsalazine |

**149. Answer is D (Methotrexate):** *Harrison 18th/ 2491; Mayo Clinic Gastroenterology and Hepatology Board Review 4th/ 177*

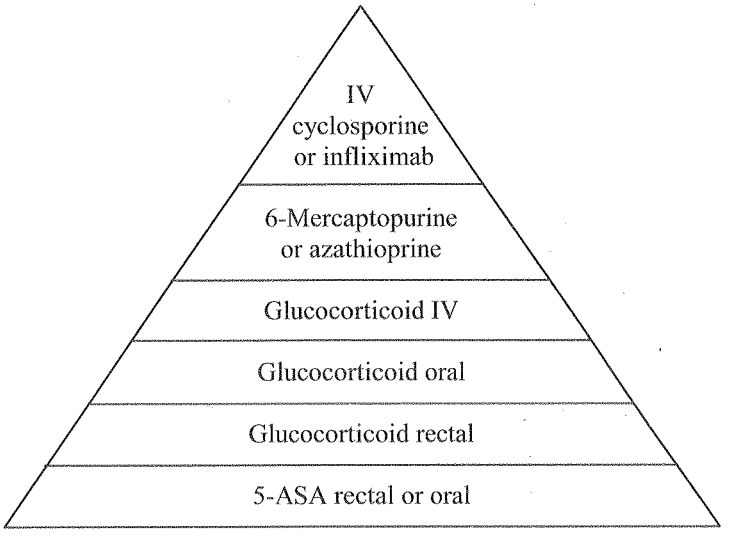
***Methotrexate has not been shown to be effective for treating active ulcerative colitis or for maintaining remission.***

| Methotrexate in Ulcerative Colitis |
|---|
| *Methotrexate has not been shown to be effective for treating active ulcerative colitis or for maintaining remission* |

| Methotrexate in Crohn's Disease |
|---|
| *Methotrexate has been shown to be effective for inducing remission in patients with steroid dependent and steroid refractory Crohn's Disease* |

| Agents that may be used for treatment of Ulcerative Colitis |
|---|
| 1. 5-ASA<br>2. Glucocorticoids<br>3. Azathioprine and 6 Mercaptopurine<br>4. Cyclosporine or TNF alpha therapy (Infliximab) |

Tacrolimus is a macrolide antibody that has shown to be effective in adults with steroid dependent or refractory Ulcerative Colitis.




**150. Answer is B (Azathioprine):** *Harrison 15th/ 1688; Harrison 16th/1785, 1786; Harrison 17th/1896; Harrison 18th/ 2490*

***Maintenance therapy with sulfasalazine was not able to maintain the patient in remission and he required corticosteroid for the control of his exacerabations. Patient is now in remission and requines a drug which can maintain him in remission.*** *Azathioprine reduces requirement of steroids in patients and maintains remission and this is thus the drug of choice here.*

This is a case of ulcerative colitis as suggested by the recurrent episodes of bloody diarrhoea.

| Clinical (1782 H/16th) | Ulcerative colitis | Crohn's disease |
|---|---|---|
| Cross blood stool | Yes | Occassionally |
| Mucus | Yes | Occassionally |

**Azathioprine & Mercaptopurine :**
Promising drugs as maintenance therapy.

*Azathioprine and 6 mercapto- purine are effective in long term management of ulcerative colitis. They reduce the requirement of steroids in patient as well as maintain the patient in remission*

**Cyclosporine:**
It is not effective in maintenance remission without 6 MP/ Azathioprine' - *Harrison*
It's greatest value is in t/t of acute severe ulcerative colitis that does not appear to be responding adequately to glucocorticoid. However it does not reduce the rate of relapse and *is not effective as maintenance therapy.*

**Methotrexate:**
Methotrexate is useful in steroid dependent patient of Crohn's disease but its role in U.C. has not been mentioned.

**Cyclophosphamide** has no role in the management of either Crohn's disease or ulcerative colitis.

**Management Protocol:**

5 Aminosalicylic acid (5ASA) derivatives

(Mainstay of therapy for both U.C. & CD)

*Uncontrolled* ↓ *Exacerbations*

Glucocorticoids

- Effective for inducing remission in both Cd & U.C
- Glucocorticoids play no role in maintenance therapy in either UC or CD
- Once clinical remission has been achieved they should be tapered.

↓ *Maintenance*

Azathioprine and 6 Mercaptopurine

- Commonly employed in management of glucocorticoid dependent IBD
- Promising role as maintenance therapy

**151. Answer is a (5-Aminosalicylic Acid):** Read text below

*The mainstay of therapy for inflammatory bowel disease remains 5- Aminosalicylic derivatives – CMDT*

## Crohn's Disease

**152. Answer is B (Crohn's Disease):** *Refer previous question*

*Skip lesions are characteristic of Crohn's Disease*

**153. Answer is A (Crohn's disease):** *Harrison 18th/p 2483, 2486 Harrison's 17th/1892, 1890*

*Chronic diarrhea in association with significant perineal disease (multiple fistulas in perenium) and Small intestinal disease (strictures/obstruction) suggests a diagnosis of Crohn's disease.*

**154. Answer is D (Terminal Ileum)**

*The terminal Ileum is the most common site of Disease in Crohn's Disease.*

| Crohn's Disease (Site of Involvement) | Ulcerative Colitis (Site of Involvement) |
|---|---|
| Crohn's Disease can affect any part of the Gastrointestinal Tract from the mouth the anus. | Ulcerative Colitis by definition is a disease limited to the colon |
| Involvement is typically discontinuous with skip lesions. | Involvement is continuous without Skip Lesions Disease typically starts in the Rectum and progresses with continuous lesions (no skip lesions) in a retrograde manner (May involve the entire colon). |
| Terminal ileum is the most commonly affected site within the Gastrointestinal tract. | Rectum is the single most commonly affected site |
| Rectum is usually spared | Terminal ileum is usually not involved *Terminal ileum is classically not involved but a small subset of patients may show inflammation of the terminal ileum (Backwash Ileitis)* |

**155. Answer is B (Crohn's disease):** *CMDT 2006/623; Harrison 16th/1781 - 1782*

*'Antibodies to the yeast 'Saccharomyces cerevisiae' (ASCA) are found in 60 - 70% of patients with Crohn's disease and 10 - 15% of patients with ulcerative colitis.' - CMDT 06th/623*

Serological markers for inflammatory bowel disease

| Perinuclear Antineutrophil Cytoplasmic Antibodies (p ANCA) | Antisaccharomyces Cerevisiae Antibodies (ASCA) |
|---|---|
| • Positive in 60 - 70% of U.C. patients (and 5 - 10% of CD patients) | • Positive in 60 - 70% of CD patients (and 10 - 15% of U.C. patients) |

- *p ANCA +ve with ASCA -ve = 97% specificity for UC*
- *p ANCA +ve with ASCA +ve = 97% specificity for CD*

| Antibody | G.I. Disorder |
|---|---|
| *Antiendomysial antibody*$^{Q}$ | *Celiac sprue* |
| *Antisaccharomyces cerevisiae antibody*$^{Q}$ | *Crohn's disease* |
| *Antineutrophilic cytoplasmic antibody*$^{Q}$ | *Ulcerative colitis* |

**156. Answer is A (Clostridium Difficle)**: *Harrison 18th/p 2480 Harrisons 17th/ 1887, Harrisons 16th /1777.*

*A possible infectious etiology includes clostridium difficle and M paratuberculosis amongst the options provided.*

***Clostridium difficle is the single best answer of choice when based on Harrisons 17th edition.***

**Role of infections in Inflammatory bowel disease (Infectious etiology)**

Infection with multiple pathogens may initiate inflammatory bowel disease (IBD) by triggering an inflammatory response that the mucosal & immune system may fail to control

| Agents According to Harrisons 16th edition (Do not mention Clostridium difficle) | Agents according to Harrisons 17th edition (Include Clostridium difficle) |
|---|---|
| • *'Multiple pathogens (Salmonella, Shigella sp. Campylobacter sp.) may initiale IBD by triggering an inflammatory response' – H/16th*<br>• *Anaerobic organisms particularly Bacterioides species may be responsible for induction of inflammation - H/16th*<br>• **Regarding M. Paratuberculosis**<br>*'Three specific agents, M. paratuberculosis paramyxovirus and Helicobacter species have received greatest attention'*<br>However<br>*M paratuberculosis does not have a confirmed disease association and antimycobacterial agents are not effective in treating CD.* | • *'Multiple pathogens (Salmonella, Shigella sp, Campylobacter sp,* ***Clostiridium difficle****) may initiate IBD by triggering an inflammatory response' – H/17th*<br>• *Anaerobic organisms particularly Bacterioides and* ***Clostridia species*** *and some aerobic species as Escherechia may be responsible for the induction of inflammation' – H/17th*<br>**Regarding M. Paratuberculosis**<br>*Harrisons 17th edition does not mention M. Paratuberculosis amongst the list of agents implicated in causing Crohn's disease.* |

**157. Answer is C (Osteoarthritis):** *Harrison 18th/p2487, 2488 Harrisons 17th/ 1893 – 1894 Refer previous question*

*Osteoarthritis is not an extraintestinal manifestation of inflammatory bowel disease*
***Uveitis, Sclerosing Cholangitis, and skin nodules*** *(Erythema nodosum) are all recognized extraintestinal manifestations of inflammatory bowel disease.*

**158. Answer is D (Pancreatitis) :** *Harrison 14th / 1642; Harrison 15th/1686-7; Harrison 16th/1783, 1784;17th/1893, 1894 Harrison 18th/p 2487, 2488*

*Pancreatitis is not associated with inflammatory bowel disease.*

**Extraintestinal diseases associated with inflammatory bowel disease:**

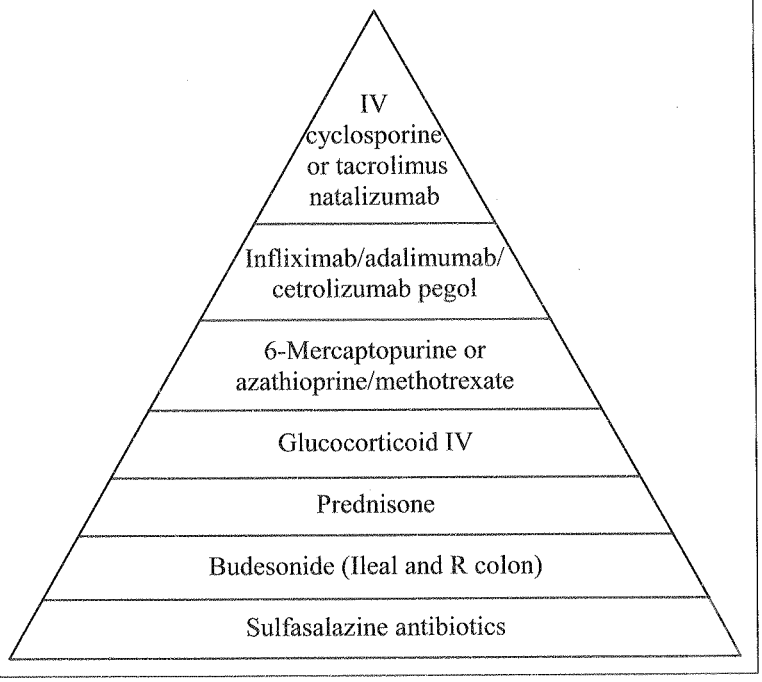
| Joint manifestations: | Ocular manifestations: | Skin manifestations: | Hepatic manifestations: |
|---|---|---|---|
| Arthralgia to acute arthritis<br>Ankylosing spondylitis<br>Sacroilitis | Episcleritis<br>Recurrent iritis<br>Uveitis | Erythema nodosum<br>Pyoderma gangrenosum$^{Q}$<br>**Aphthous ulcers** | Nonspecific focal hepatitis<br>Fatty liver<br>Pericholangitis<br>**Sclerosing cholangitis**<br>Autoimmune chronic active hepatitis<br>**Cirrhosis** |

**159. Answer is C (Natalizumab):** *Harrison 18th/ 2492; Mayo Clinic Gastroenterology and Hepatology Board Review 4th/ 177*

***Natalizumab is a monoclonal antibody shown to be useful for Crohn's Disease.***

*Natalizumab is a recombinant humanized immunoglobulin G4 Antibody (IgG4 Monoclonal Antibody) against alpha 4 integrins that is effective in the induction and maintenance of remission in Crohn's Disease patients. It has been approved for the treatment of patients with Crohn's disease refractory to intolerant to anti-TNF Therapy.*

| |
|---|
| ***Omalizumab*** *is used for Bronchial Asthma (Allergic Bronchial Asthma)*<br>***Palivizumab*** *is used in infection with Respiratory Syncytial Virus (RSV)* |

| Agents that may be used for treatment of Crohn's Disease | |
|---|---|
| 1. 5-ASA<br>2. Glucocorticoids<br>3. Azathioprine and 6 Mercaptopurine (or Methotrexate)<br>4. TNF alpha Therapy (Infliximab; Adalimumab; Certolizumab)<br>5. Cyclosporine or Tacrolimus or Natalizumab |  |

Note :

Natalizumab therapy has been associated with the development of multifocal leukoencephalopathy, a predominantly fatal infection of the central nervous system by the JC polyomavius. This risk appears to be 1 in 1,000 patients, particularly those receiving treatment with several immunosuppressive agents.

## Colonic Disorders

### Irritable Bowel Syndrome (IBS)

**160. Answer is C (Rectal Bleeding):** *Harrison 18th/p2496, 2497 Harrison's 17th/1899, 1900*

***Irritable Bowel syndrome is characteristically not associated with rectal bleeding.***

*Evidence of blood in stool should raise an alarm that a process other than IBS is operating and should prompt further investigations.*

***Abdominal pain, abnormal stool formation (hard/constipation or loose/ watery stool), and Bloating*** *or feeling of abdominal distension are characteristic features of Irritable Bowel Syndrome.*

**Symptoms that cumulatively support the diagnosis of Irritable Bowel Syndrome:**

- *Abnormal stool frequency[Q] (for research purposes, "abnormal" defined as > 3 bowel movements/week)*
- *Abnormal stool formation[Q] (lumpy/hard or loose/watery stool)*
- *Abnormal stool habits[Q] (straining, urgency, or feeling of incomplete evacuation)*
- *Passage of mucus[Q]*
- *Bloating or feeling of abdominal distention*

*The diagnosis of a functional bowel disorder always presumes the absence of a structural or biochemical explanation for the symptoms.*

**Diagnostic criteria for Irritable Bowel Syndrome**

Recurrent abdominal pain or discomfort at least 3 days per month in the last 3 months associated with two or more of the following

1. *Improvement with defecation[Q]*
2. *Onset associated with a change in frequency of stool[Q]*
3. *Onset associated with a change in form (appearance) of stool[Q].*

*Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis.*
*Discomfort means an uncomfortable sensation not described as pain. In pathophysiology research and clinical trails, a pain/discomfort frequency of at least 2 days a week during screening evaluation is required for subject eligibility.*

**161. Answer is C (Abdominal distension):** *Harrison 18th/p 2496, 2497 Harrison's 17th/1900; Refer previous question*

*Bloating or feeling of abdominal distension is a characteristic feature of Irritable bowel syndrome.*

*Presences of blood in stool, weight loss or anorexia are 'Red Flag' conditions in irritable bowel syndrome. Their presence should raise on alarm that a process other than IBS is operating and should prompt further investigations to rule out other disease process.*

**"Red flag" conditions in irritable bowel syndrome that suggest possibility of another disease**

Presence of any of the following calls for further investigation to rule out other disease processes:

- *Fever*
- *Blood in stools*
- *Nocturnal pain*
- *Abnormal physical findings*
- *Onset in patients>50 years of age*
- *Weight loss or anorexia*
- *Anemia*
- *Abnormal blood studies*
- *Family history of inflammatory bowel disease or malignancy*

**162. Answer is A (Irritable bowel syndrome):** *Harrison 18th/p 2496, 2497, 2498 Harrison's 17th/- 1899, 1900, 1901; 'Sleisenger's and Fordtran's 'Gastrointestinal & Liver Disease' 8th/ed 2634*

***Stress related increase in abdominal pain with change in bowel habit and passage of mucus in stool, together with absence of 'red flag' signs such as blood in stool in a 'young female' suggest a diagnosis of Irritable bowel syndrome.***

**Young age and Female sex are epidemiological risk factors for IBS**

"Younger people have a higher prevalence of IBS in the community"
*Although IBS may affect all ages most patients have their onset of symptoms before age of 45. Older people have a lower rate reporting frequency and onset in patients > 50 years of age is a 'Red Flag' sign that may suggest the possibility of another disease*
*'Women are diagnosed two or three times as often as men and make up 80% of the population with severe IBS'*
*– Harrison 17th/1899*

**Onset of symptoms in periods of stress support a diagnosis of IBS.**
*Onset of symptoms in periods of stress or emotional upset are suggestive of IBS' - Harrison 17th/ed 1901*

**IBS is charachteristically associated with absence of blood in stool**
*Presence of blood in stool is a 'Red Flag' sign that suggests possibility of another disease. - Harrison's 17th/1901*

**"Red flag" conditions in irritable bowel syndrome that suggest possibility of another disease**

Presence of any of the following calls for further investigation to rule out other disease processes:

- *Fever*
- *Blood in stools*
- *Nocturnal pain*
- *Abnormal physical findings*
- *Onset in patients>50 years of age*
- *Weight loss or anorexia*
- *Anemia*
- *Abnormal blood studies*
- *Family history of inflammatory bowel disease or malignancy*

**Abdominal pain with change in bowel habit together with passage of mucus in stool (in the absence of 'Red Flag' signs) supports a diagnosis of IBS.**

| Symptoms that cumulatively support the diagnosis of Irritable Bowel Syndrome: |
|---|
| • *Abnormal stool frequency[Q] (for research purposes, "abnormal" defined as > 3 bowel movements/week)* |
| • *Abnormal stool formation[Q] (lumpy/hard or loose/watery stool)* |
| • *Abnormal stool habits[Q] (straining, urgency, or feeling of incomplete evacuation)* |
| • ***Passage of mucus[Q]*** |
| • *Bloating or feeling of abdominal distention* |

**163. Answer is E (Predisposes to malignancy in long term):** *Harrison 18th/p 2496, 2497 Harrisons 17th / 1899, 1990*

*Irritable Bowel syndrome (IBS) is a benign functional bowel disorder.*
*IBS does not predispose to malignancy in the long term*

**IBS may be associated with diarrhea or constipation**
*'The most common pattern in IBS is constipation alternating with diarrhea' - Harrison*

**IBS may be associated with Anxiety and stress**
*Abnormal Psychiatric manifestation are recorded in 80% of IBS patients.*
*Emotional disorder and stress are associated with exacerbation of symptoms in IBS*

**164. Answer is A (Lubiprostone):** *Harrison's 18th/2500, 2501*

***Lubiprostone is an effective agent for treatment of patient with constipation predominant Irritable Bowel Syndrome.***
***Lubiprostone** is a novel chloride channel activator that stimulates chloride channels in the apical membrane of intestinal epethelial cells. Chloride secretion induces passive movement of sodium and water into the bowel lumen and improves constipation predominant IBS.*

**Cholestyramine and Alosetron** *are used for the management of patients with Diarrhea predominant Irritable Bowel Syndrome.*

**Rifaximin** is a non-absorbed oral antibiotic being evaluated for global Irritable Bowel Syndrome Symptoms. *It is not specific for constipation predominant IBS* and currently there is still insufficienct data to recommend routine use of this antibiotic in the treatment of IBS.

**Possible Drugs for a Dominant Symptom in IBS:** *(Harrison's 18th/2501)*

| Diarrhea | Constipation | Abdominal Pain |
|---|---|---|
| • *Lopepramide* | • *Psyllium husk* | • *Smooth-muscle relaxant* |
| • *Cholestyramine resin* | • *Methylcellulose* | • *Tricyclic antidepressants* |
| • *Alosetron* | • *Calcium polycarbophil* | • *Selective serotonin reuptake inhibitors* |
| | • *Lactulose syrup* | |
| | • *70% sorbitol* | |
| | • *Polyethylene glycol 3350* | |
| | • *Lubiprostone (Amitiza)* | |
| | • *Magnesium hydroxide* | |

## Diarrhea and Colitis

**165. Answer is A (Bacillus cereus):** *Harrison 17th /248; Harrison's 18th/311*

***Bacillus cereus causes non invasive diarrhea secondary to small bowel hypersecretion, as a result of preformed bacterial toxins.***
*Rotavirus, Aeromonas sp and Shigella are all invasive organism known to cause invasive diarrhea.*

Association between Pathobiology of Causative Agents and Clinical Features in Acute Infectious Diarrhea:

**Toxin Producers (Diarrhea from Hypersecretion)**

| Pathobiology/Agents |
|---|
| Preformed toxin |
| • *Bacillus cereus* |
| • *Staphylococcus aureus* |
| • *Clostridium perfringens* |
| Enterotoxin |
| • *Vibrio cholera* |
| • *Enterotoxigenic Escherichia coli* |
| • *Klebsiella pneumonia* |
| • *Aeromonas* species |
| Enteroadherent |
| • Enteropathogenic and Enteroadherent *E. coli* |
| • *Giardia* organisms |
| • Cryptosporidiosis |
| • Helminths |
| Cytotoxin producers |
| • *C. difficile* |
| • Hemorrhagic *E. coli* |

**Invasive Organisms (Invasive Diarrhea)**

| |
|---|
| Minimal inflammation |
| • Rotavirus and norovirus |
| Variable inflammation |
| • *Salmonella* |
| • *Campylobacter* |
| • *Aeromonas* species |
| • *Vibrio parahaemolyticus* |
| • *Yersinia* |
| Severe inflammation |
| • *Shigella* species |
| • Enteroinvasive *E. coli* |
| • *Entamoeba histolytica* |

Association between Pathobiology of Causative Agents and Clinical Features in Acute Infectious Diarrhea:

**Toxin Producers (Diarrhea from Hypersecretion)**

| Pathobiology/Agents | Incubation Period | Vomiting | Abdominal Pain | Fever | Diarrhea |
|---|---|---|---|---|---|
| Preformed toxin | | | | | |
| *Bacillus cereus, Staphylococcus aureus, Clostridium perfringens* | 1–8 h<br>8–24 h | 3–4+ | 1–2+ | 0–1+ | 3–4+, watery |
| Enterotoxin | | | | | |
| *Vibrio cholerae, Enterotoxigenic Escherichia coli, Klebsiella pneumoniae, Aeromonas* species | 8–72 h | 2–4+ | 1–2+ | 0–1+ | 3–4+, watery |
| Enteroadherent | | | | | |
| Enteropathogenic and Enteroadherent *E. coli, Giardia* organisms, cryptosporidiosis, helminths | 1–8 d | 0–1+ | 1–3+ | 0–2+ | 1–2+, watery, mushy |
| Cytotoxin producers | | | | | |
| *C. difficile* | 1–3 d | 0–1+ | 3–4+ | 1–2+ | 1–3+, usually watery, occasionally bloody |
| Hemorrhagic *E. coli* | 12–72 h | 0–1+ | 3–4+ | 1–2+ | 1–3+, initially watery, quickly bloody |

**Invasive Organisms (Invasive Diarrhea)**

| | | | | | |
|---|---|---|---|---|---|
| Minimal inflammation | | | | | |
| Rotavirus and norovirus | 1–3 d | 1–3+ | 2–3+ | 3–4+ | 1–3+, watery |
| Variable inflammation | | | | | |
| *Salmonella, Campylobacter*, and *Aeromonas* species, *Vibrio parahaemolyticus, Yersinia* | 12 h–11 d | 0–3+ | 2–4+ | 3–4+ | 1–4+, watery or bloody |
| Severe inflammation | | | | | |
| *Shigella* species, Enteroinvasive *E. coli, Entamoeba histolytica* | 12 h–8 d | 0–1+ | 3–4+ | 3–4+ | 1–2+, bloody |

**166. Answer is B (Increased Chloride Secretion into the intestine)**

***Pathophysiology of the secretory diarrhea is best explained by active chloride secretion or inhibited sodium absorption.*** An increase of cellular cyclic Adenosine Monophosphate (cAMP) results in activation of cytoplasmic kinases. Two important consequences of this are, stimulation of chloride secretion through chloride channels and inhibition of neutral Na/Cl absorption. These phenomena typically result in massive secretory diarrhea

Active chloride secretion or inhibited sodium absorption, which create an osmotic gradient favourable for the movement of fluids from blood to lumen, explains the pathophysiology of the secretory diarrhea. Agents that increase enterocyte cyclic adenosine monophosphate CAMP (e.g., cholera toxin, prostaglandin), cyclic Guanosine monophosphate (cGMP) (e.g., Escherichia coli stable toxin), or intracellular ionized calcium ($Ca^{2++}$) (e.g., acetylcholine) inhibit Na absorption and stimulate Cl secretion

**167. Answer is D (Clostridium Difficle):** *Manual of Gastroentrology 4th 4th/184 - Harrison 18th/p311 Harrisons 17th/249*

*Clostridium difficle is typically associated with Inflammatory' diarrhea and not 'secretory' diarrhea.*

*Clostridium Difficle may rarely cause a secretory type of diarrhea, but it remains the single best answer of exclusion.*

**Causes of Secretory Diarrhea**

| Enterotoxins Produced by infectious organisms | Laxatives | Harmone Producing Tumors | Others |
|---|---|---|---|
| • ***Vibrio cholerae*** | ***Exogenous Laxatives*** | • Carcinoids (serotonin) | • Chronic Ethanol ingestion |
| • Enterotoxigenic E coli (ETEC) | • Castor oil | • VIP omas | • Bowel Rescetion, disease or fistula (↓ absorption) |
| • Staphylococcus Aureus | • ***Phenolpthalein*** | • Medullary cancer Thyroid (calcitonin) | • Partial bowel obstruction or fecal impaction |
| • Bacillus cereus | • Bisacodyl | • Gastrinoma (ZES) | • Addison's disease |
| • Rota virus | • Senna | • Mastocytosis (Histamine) | • Congenital electrolyte absorption defects |
| | • Dioctyl sodium sulphosuccinate | • Colorectal villous adenoma | |
| | ***Endogenous Laxatives*** | | |
| | • Bile salts (Bile duct obstruction) | | |
| | • Fatty acids (Pancreatic insufficiency small Intestinal mucosal disease) | | |

**168. Answer is B (Celiac Disease):** *Harrison 18th / 313*

*Celiac Disease is associated with Steatorrheal diarrhoea from mucosal malabsorption.*

| Secretory Diarrhea | Steatorrheal Diarrhea |
|---|---|
| ▪ Certain Bacterial Infection<br>  ○ Vibrio Cholera<br>  ○ Enterotoxigenic E.Coli<br>▪ Non Osmotic Stimulant Laxatives<br>▪ Hormone Producing Endocrine Tumors<br>  ○ Carcinoid,<br>  ○ VIPomas,<br>  ○ Gastrinomas,<br>  ○ Medullary Carcinoma Thyroid (Calcitonin)<br>▪ Bile acids (endogenous laxatives)<br>▪ Bowel resection / disease or fistula<br>▪ Addison's Disease<br>▪ Congenital Electrolyte Absorption defects<br>▪ Chronic Alcohol Ingestion<br>▪ Diabetic Diarrhea | • Intraluminal maldigestion<br>  ○ Pancreatic exocrine insufficiency,<br>  ○ Bacterial overgrowth,<br>  ○ Bariatric surgery,<br>  ○ Liver disease<br>• Mucosal malabsorption<br>  ○ Celiac sprue,<br>  ○ Whipple's disease,<br>  ○ Infections,<br>  ○ Abetalipoproteinemia,<br>  ○ Ischemia<br>• Postmucosal obstruction (1° or 2° lymphatic obstruction) |

**169. Answer is C (Osmolar gap < 50 ):** *Mayo Clinic Internal Medicine Review 7th/ 262,263,264*

*Osmotic Diarrhoea is typically associated with a high osmolar gap typically more than 100. The normal stool osmolar gap is less than 50.*

| Feature | Osmotic diarrhea | Secretory diarrhea |
|---|---|---|
| Mechanism | Osmotic diarrhea occurs when water-soluble molecules are poorly absorbed, remain in the intestinal lumen and retain water in the intestine. | In secretory diarrhea, fluid and electrolyte transport is abnormal. That is, the intestine secretes rather than absorbs fluid |
| Daily stool volume (Liters) | <1 | >1 |
| Effect of 48 hour fasting | Diarrhea stops | Diarrhea continues |
| Fecal fluid analysis | | |
| Solute gap | >100 | <50 |

**170. Answer is A (Large Stool Volume):** *Mayo Clinic Internal Medicine Review 7th/ 262,263,264*

***Large Bowel Colonic Diarrhoea is typically associated with frequent small volume stools since reservoir capacity of the bowel is reduced.***

*Right-sided (Small Bowel) diarrhea is characterized by large-volume stools. The increase in the number of stools is modest and symptoms attributed to inflammation of the recto-sigmoid are absent. Left-sided (Colonic) diarrhea is characterized by frequent, small-volume stools with obvious evidence of inflammation*

**Right-Sided and Left-Sided Diarrhea: Contrasts in Clinical Presentation**:

| Feature | Small-bowel Diarrhea (Right-sided) | Large Bowel Colonic diarrhea (Leftt-sided) |
|---|---|---|
| Reservoir capacity | Intact | Decreased |
| Stool volume | Large | Small |
| Increase in number of stools | Modest | Large |
| Urgency | Absent | Present |
| Tenesmus | Absent | Absent |
| Mucus | Absent | Absent |
| Blood | Absent | Present |
| Proctosigmoidoscopy | Usually Normal | Usually Confirms Inflammation |
| Mechanism | Non-Specific | Usually Exudative |

**171. Answer is C (Abetalipoproteinemia):** *Clinical Hepatology: Principles and Practice of Hepatobiliary Diseases (Springer) 2009/ 1184; Merritt's Neurology (Lippincott Williams & Wilkins, 2010) 12th/ 665,666; The 5-Minute Neurology Consult (Lippincott Williams & Wilkins) 2012/ 452; Neonatology: A Practical Approach to Neonatal Diseases (Springer) 2012/ 951*

***The finding of acanthocytes on blood smear of a child with Steatorrhea or chronic diarrhoea should point to the diagnosis of Abetalipoproteinemia.*** *Acanthocytosis with diarrhoea may also be seen in Wolman's disease.*

**Diarrhoea with acanthocytosis may be seen in Abetalipoproteinemia and Wolman's Disease**

| Condition | Enzyme Deficiency | Clinical Features | Acanthocytes | Age of onset |
|---|---|---|---|---|
| Abetalipoproteinemia (Bassen-Kornzweig Disease) | Micsomal Triglceride Transfer Protein (MTP) Large subunit of protein is absent | Diarrhea with fat malabsorption (Staetorrhoea), Failure to thrive, Prominent neurological involvement with Retinitis pigmentosa and ataxia | Present | Neonatal Period |
| Wolman Disease (Cholesterol Ester Storage Disease) | Lysosomal Acid Lipase | Diarrhea with malabsorption Failure to thrive Hepatosplenomegaly Neurological involvement is mild Adrenal Calcification is typical | Present (Vacuolated Lymphocytes are typical) | Neonatal Period |

**Abetalipoproteinemia;**

| Inheritance and Deficiency |
|---|
| Abetalipoproteinemia is as rare autosomal recessive conditions characterized by a deficiency of Microsomal Triglyceride Transfer Protein (MTP) (Large subunit of protein is absent) that results in lack of lipoproteins. |
| Presentation |
| • Gastrointestinal Symptoms: Affected children typically present with severe fat malabsorption from birth with abdominal distension, failure to thrive, and deficiency of fat-soluble vitamin deficiencies.<br>• Neurological findings: Prominent with Retinitis Pigmentosa, Ataxia, intention tremors, loss of position and vibration sense. |
| Diagnosis |
| The diagnosis may be made by<br>• Demonstration of acanthocytes in the peripheral blood smear; and<br>• Low to absent levels of triglycerides, cholesterol, chylomicrons, low-density lipoproteins (LDL), and very low-density lipoproteins (VLDL) in the blood |
| Treatment |
| Treatment is supportive<br>• Decrease long –chain fatty acids in the diet (supplement with medium chain triglycerides)<br>• Supplement fat soluble vitamins ADEK. |

**172. Answer is C (Wolman's Disease):** *Clinical Hepatology: Principles and Practice of Hepatobiliary Diseases (Springer) 2009/ 1184; Merritt's Neurology (Lippincott Williams & Wilkins, 2010) 12th/ 665,666; The 5-Minute Neurology Consult (Lippincott Williams & Wilkins) 2012/ 452; Neonatology: A Practical Approach to Neonatal Diseases (Springer) 2012/ 951*

*The finding of acanthocytes on blood smear of a child with Steatorrhea or chronic diarrhoea should point to the diagnosis of Abetalipoproteinemia.* ***Acanthocytosis with diarrhoea may also be seen in Wolman's disease***

**Wolman disease**:

- Wolman Diseases is a Cholesterol Ester Storage disease characterized by a deficiency of the enzyme, Lysosomal Acid Lipase (Mapped to a gene on chromosome 10q23.2.
- It is characterized by the accumulation of cholesterol esters and triglycerides in affected tissues
- Infants are normal as birth, but have rapid onset of severe vomiting abdominal distention, malabsorption with diarrhea, poor weight gain, jaundice, fever, diffuse rash hepato-splenomegaly, and adrenal insufficiency (Adrenal calcification is noted on radiographs)
- Neurological involvement may be seen though it is generally mild and includes delayed intellectual development and mild spasticity
- Acanthocytosis may be seen. Lysosomal fat vacuoles are typically seen in hepatocytes and lymphocytes (Kupffer cells; Foam cells ;intensely PAS-Positive).On Polarizing Microscopy cholesterol crystals display birefringence (Maltese Crosses)
- The course is generally quite rapid. Death occurs within 3 to 6 months in most cases; no treatment is available.

**173. Answer is C (Reduces with fasting):** *CMDT 2009/499; Manual of Gastroenterology 4th/184 – Harrison 18th/p 312 Harrisons 17th/249*

*Secretory diarrhea does not reduce with fasting.*
*In secretory diarrhea an abnormal ion transport occurs accross intestinal epethelial cells. This diarrhea is not related to the intestinal content and hence it typically does not cease with fasting.*

| Typical Features of Secretory Diarrhea |
|---|
| • ***Large volume (typically > 1L/ day)*** |
| • ***Little change with fasting*** *(Diarrhea typically does not cease while patient fasts)* |
| • ***Normal stool osmotic gap*** *(osmoality of stool is close to osmolality of plasma)* |
| • *No anion gap* |
| • *Stools are watery in consistency and do not contain pus or blood* |
| • ***Painless*** |

**174. Answer is A, B, and C (Febrile dysentery with fever ≥ 38.5; Immunocompromised patient; Elderly patient):** *Harrisons 17th/248, 249*

*Antibiotic coverage is indicated whether or not a causative organism is discovered in patients who are **immuncompromized**, have mechanical heart valves or recent vascular grafts or **are elderly**. Emperical antibiotic treatment should also be started in **moderately to severely ill patients with febrile dysentery** specially when fever ≥ 38.5°C*

Indications for Antibiotic coverage

- Patients who are immuno *compromised*$^{Q}$
- Patients with *mechanical heart valves*$^{Q}$
- Patients with *recent vascular grafts*$^{Q}$
- Patients who *are elderly*$^{Q}$
- Moderately to severely ill patients with *fibrile dysentry*$^{Q}$ (Grossly bloody stools and fever ≥ 38.5°C)
- Increased fecal WBCS

**175. Answer is C (Antibiotic Therapy):** *Essentials of Clinical Infectious Diseases By William Floyd Wright (Demos Medical Publishing), 2013*

***Overgrowth of Clostridium difficile*** is typically associated with ***Pseudomembranous colitis. The most important risk factor for Clostridium Difficile Pseudomembranous Colitis is Antibiotic Therapy. Antibiotic use causes an alteration of the normal colonic flora leading to an overgrowth of C. difficile bacteria.***

**176. Answer is B (Clostridium Difficile)**

*Pseudomembranous colitis is most commonly caused by Clostridium difficile in the setting of antibiotic therapy. **Pseudomembranous colitis**, also known as antibiotic associated colitis is an inflammatory process of the colon that is almost always associated with an overgrowth of the bacterium Clostridium difficile, C. Difficile is an anaerobic, gram-positive bacterium that is highly transmissible.*

***The first antibiotic linked to Pseudomembranous colitis is Clindamycin***

**177. Answer is A (Clindamycin):** *Elective General Surgery: An Evidence-Based Approach 2nd/383*

*Clindamycin was the first antibiotic to be clearly associated with pseudomembranous colitis.*
*'The first antibiotic linked to pseudomembranous colitis is clindamycin'- Oxford Handbook of Practical Drug Therapy*

**178. Answer is B (Enterotoxigenic E.Coli):** *Travel Medicine (Elsevier Health Sciences) 3rd/ 179*

*Enterotoxigenic E.Coli (ETEC) is the single most common cause of travellers' diarrhea in the world.*

***Bacteria are the most common cause of Travellers' Diarrhea and ETEC is the single most common Pathogen***

**179. Answer is B (Longitudinal ulcers):** *Harrison 18th/1276; Current Diagnosius & Treatment in Infectious Diseases (International Edition)/561; Robin's Pathology 6th/359; Differential Diagnosis in INternal Medicine: From Symptom to Diagnosis (Thieme) 2007/148; 'Fundamentals of Surgical Pathology' by Shariff (Jaypee)/179*

***Typhoid ulcers (Salmonella/Enteric Fever) occur due to ulceration of Peyer's patches. Since Peyer's patches (aggregation of lymphoid follicles in the wall of gut) are oval in shape and placed longitudinally/vertically along the antimesenteric border, the axis of typhoid ulcers is longitudinal.***

*History of prolonged fever and abdominal discomfort together with typical features of splenomegaly and leucopenia suggest a diagnosis of salmonelosis or 'Enteric Fever'. Enteric fever is a potentially fatal systemic illness and death may occur from life threatening complications of gastrointestinal bleeding and intestinal perforation. This most commonly occurs in the third or fourth week of illness and results from hyperplasia ulceration (longitudinal) and necrosis of the ileocecal Payer's patches at the initial site of salmonella infiltration.*

| Typhoid Ulcers (Enteric Fever) | Tubercular Ulcers |
|---|---|
| • Longitudinal Ulcers (as they occur over lymphoid follicles/Peyer's patches at the antimesenteric border)<br>• When they heal, they cause no features of obstruction | • Transverse ulcers (due todirection of lymphatics)<br>• When they heal they cause stenosis and obstruction due to fibrosis (since they are circular surroundings the lumen of intestine) |

**Enteric Fever**

Enteric Fever is a potentially life threatening systemic disease characterized by fever and abdominal pain caused by dissemination of Salmonella Typhi or Salmonella Parotyphi.

| Typical Hallmark Features | Non specific symptoms | Typical Findings (Signs typical, but not always present) |
|---|---|---|
| • ***Fever***<br>• ***Abdominal Discomfort*** (Pain, Anorexia, Diarrhea or Constipation, Anorexia, Nausea, Vomiting) | • Headache<br>• Chills/Shivering<br>• Cough<br>• Sweating<br>• Myalgia<br>• Arthralgia<br>• Fatigue | • Rose spots<br>• ***Splenomegaly***<br>• ***Leucopenia*** with a distinct left shift<br>The lipopolysacharide endotoxin of bacteria is responsible for Leucopenia and splenomegaly<br>• Relative Bradycardia dispite high fever<br>• Mental state changes (Typhoid Psychosis) (Muttering Delerium/Coma vigil) |

Life threatening complications primarily include ***Gastrointestinal Bleeding and/or Gastrointestinal Perforation*** which most frequently occur in the third or fourth week of illness from hyperplasia, ulceration and necrosis of the ileocoecal Payer's patches at the initial site of Salmonella infection

**180. Answer is B (Intravenous Metronidazole):** *Harrisons 16th/1214, 1216-1217; Harrison 17th/1278; 18th/p 1686*

*Presence of the classic flask shaped ulcers' in a patient presenting with lower gastrointestinal bleeding suggests a diagnosis of 'Intestinal amebic colitits'.*

***'Patients with amebic colitis should be treated with intravenous or oral Metronidazole.'*** *- Harrisons 16/e, p 1217*

**Intestinal Amebiasis (Amebic colitis)**

| Pathology (H 16/e, 1214) | Clinical features (H 16/e, 1215) | Treatment (H 16/e, p 1217) |
|---|---|---|
| • Microulcerations of the mucosa of cecum, sigmoid colon and rectum<br>↓<br>• Small ulcers will heaped up margins and normal intervening mucosa<br>↓<br>• ***Classic 'Flask-shaped' ulcers***[Q] Produced by submucosal extension of ulceration under viable appearing surface mucosa | • Lower abdominal pain<br>• Diarrhea<br>• Dysentry : stools contain little fecal matter and consist ***mainly of blood and mucus***<br>• Systemic features such as malaise weight loss, fever<br>• ±Toxic megacolon<br>• ±Tender abdominal mass (Ameboma) | ***Metranidazole (Intravenous or oral)***<br>+<br>Luminal agents<br>• Iodoquinol<br>'Paramomycin' |

**181. Answer is B (ELISA) :** *Ghai 5th/221*

*In Extra-intestinal amebiasis, antibody detection by ELISA is the most sensitive test - Ghai 5th/221.*

ELISA : This test is positive in more than 90% of patients and it usually reverts to normal with in 6-12 months.
IHA : May also be done in invasive Amoebiasis or liver abscess.
*The interpretation of the IHA is however more difficult because titres may remain positive for as long as 10 years.*

**182. Answer is C (Stricture and obstruction);** *Gastrointestinal Pathology by Chandrasoma(1998)/199; 'Typhoid Fever' by Khosla 1st/149*

*Strictures and obstruction do not occur in typhoid ulcers.*

*'Typhoid Ulcers heal without significant scarring in patients that recover and hance do not produce strictures or intestinal obstruction' – Gastrointestinal Pathology*

Characteristic Features of Typhoid Ulcers

- Most common site is mucosa of small intestine (Ileum) in region of lymphoid patches (Payer's patches)
- Ulcers are *oval*
- Ulcers are arranged *longitudinally (Longitudinal ulcers)*[Q]
- Lie in the long axis of the intestine along the *antimesenteric border*[Q]
- Ulcers may be single or multiple
- Ulcers may erode and cause complications *(Bleeding/perforation)*[Q]
  - Bleeding
  - Perforation
- ***Ulcers heal without significant scarring or fibrosis in patients who recover***
  - Strictures and intestinal obstruction almost never occurs.

**183. Answer is D (Neutropenic Colitis) :** *Harrisons 16th/492*

*Acute Right sided lower quadrant pain following chemotherapy in an immunocompromised host in characteristic of Neutropenic colitis.*

**Typhilitis : Syn : Neutropenic colitis,** Necrotizing colitis, Necrotizing enteropathy, ileocoecal syndrome or cecitis.

- This syndrome is classically seen in neutropenic patients after chemotherapy with cytotoxic drugs
- More common in children than adults
- More common in patients with AML/ALL than among those with other types of cancer.

- Clinically characterized by
  - Fever
  - ***Right lower quadrant pain and tenderness (Most characteristic)***
  - Associated bloody diarrhea (±)
  - Immunocompromised blood picture
- Confirmed on CT/USG Finding a thickened coecal wall.

## Colorectal Carcinomas

**184. Answer is A (Familial polyposis) :** *Harrison 15th / 582; Harrisons 16th/528, 529; Harrison 17th/574, 575 Harrison 18th/p 768, 769, 770*

*'Familial polyposis of colon' is characterized by the appearance of thousands of adenomatous polyps throughout the large bowel. If polyposis is not treated surgically, colorectal cancer will develop in almost all patients before the age of 40. Once the multiple polyps that constitute 'Polyposis' are detected patients should undergo total colectomy*

**Remember :**

| **Non-malignant polyps**[Q] (Rare/Small Malignant potential) | |
|---|---|
| ***Hamartomatous polyps***[Q] | ***Hyperplastic polyps***[Q] |
| *Juvenile* ***polyposis***[Q]<br>*Peutz Jeghers syndrome*[Q] | |

| **Malignant polyps**[Q] |
|---|
| *Adenomatous Polyps*[Q] |
| ***Familial adenomatous polyposis***[Q]<br>*Gardner's syndrome*[Q]<br>*Turcot's syndrome*[Q]<br>*Lynch syndrome*[Q] |

**185. Answer is B (Familial Polyposis coli) :** *Harrison's 15 th/582; Harrison 16th/528; Harrison 17th/574, 575 Harrison 18th/p 768, 769, 770*

*Familial polyposis coli if not treated surgically, colorectal cancer will develop in almost all patients before age 40. - Harrison*

***Familial polyposis coli*** *is a rare condition characterised by appearance of thousands of adenomatous polyps throughout the large bowel. Colonic polyps are rarely present before puberty but are generally evident in affected individuals by 25 years of age. If polyposis coli is not treated surgically, colorectal cancer will develop in almost all patients before age 40. – Harrison*

**Review of Hereditary gastrointestinal polyposis syndromes**

**Hereditary *autosomal dominant*[Q] gastrointestinal polyposis syndromes**

↓

| **High Malignant Potential**[Q] *(histologically adenomas*[Q]*)* | | |
|---|---|---|
| Syndrome | **Distribution** | **Associated** |
| **Familial colonic Polyposis** | Large intestine | None |
| **Gardner's syndrome** | *Large intestine > small intestine* | Osteomas<br>Lipomas<br>Fibromas<br>Epidermal cyst<br>*Ampullary Ca*<br>Desmoid |
| **Turcot's syndrome** | Large intestine | Brain Tumours |

↓

| **Rare (small) Malignant Potential**[Q] *(histologically hamartomas*[Q]*)* | | |
|---|---|---|
| **Syndrome** | **Distribution** | **Associated** |
| **Peutz Jagher's syndrome** | SI > LI > Stomach | **Mucocutaneous pigmentations**<br>Tumours of ovary, Breast, pacnreas, endometrium |
| **Juvenile polyposis syndrome** | LI > SI > Stomach | Various congenital abnormalities |

**186. Answer is D (Familial Polyposis Coli):** *Harrison 18th/p 768, 769, 770*

*The strongest corelation with colorectal cancer is seen in Familial Adenomatous Polyposis (FAP).*

*Familial Adenomatous Polyposis (FAP) is a rare autosomal dominant condition characterized by the development of thousands of adenomatous polyps throughout the large intestine. Virtually 100 percent of patients with Familial Adenomatous Polyposis will develop colorectal carcinoma if not treated surgically with total colectomy.*

**187. Answer is A (Juvenile Polyps):** *Sabiston 17th / 1451 – 1454*

*Juvenile Polyps is the single best answer of choice.*

*Juvenile polyps (sporadic), in general occur singly and being hamartomatous lesions have no malignant potential-Robbins* ***Juvenile polyps are benign polyps*** *- Sabiston*

**Pathologically hamartomas are considered benign and devoid of malignant potential. However hamartomatous polyps associated with Autosomal dominant hereditary syndromes have now been established to carry a small malignant potential** *(Rare)*

- ***Juvenile Polyps are benign but Juvenile Polyps in association with Juvenile Polyposis syndrome carry small malignant potential.***

  The juvenile polyps in Juvenile polyposis syndrome are usually hamartomas but they may contain adenomatous elements and may progress to adenomas. This syndrome is associated with increased risk of (9 – 25%) of colorectal cancer. Mutation in Tumor supressor gene SMAD4 are believed to cause 50 % of Reported cases.

- ***Sporadic Hamartomatous polyps are benign but Hamartomas in association with Peutz Jaghers Syndrome may carry a small malignant potential.***

  *Peutz Jaghers Syndrome is associated with increased risk (2-10%) of cancer in the intestinal tract. (Sabiston) The malignant potential of polyps associated with Peutz Jaghers Syndrome is small – CSDT.*

**188. Answer is A (Ulcerative colitis):** *Robbins 7th/ 849*

*Malignant potential is seen in both ulcerative colitis and Crohn's disease, but ulcerative colitis is a more important risk factor than Crohn's and hence the answer of choice here. Diverticular disease and ischaemic colitis do not predispose to cancer.*

***The risk of cancer in CD is considerably less than in patients with chronic U.C.'*** *– Robbins.*

Confusing fact:

- The cancer risk in CD and UC are probably equivalent for similar extent and duration of disease – *Harrison 16th/ 1788*
- Patients with Crohn's pancolitis have similar risk – *Schwartz 8th/ 1085*

*Thus while certain texts are now suggesting that the cancer risk for both CD & UC are probably equivalent, these are other texts which identify U.C. as a significantly more important cause. As we have to pick one single best answer, the option of choice remains U.C.*

**189. Answer is C (Peutz-Jegher's Syndrome):** *Harrison's 17th/326; Harrison's 16th/302; Robbins 7th/859, 1189; Sternberg's diagnostic surgical pathology 4th/1548*

*Mucocutaneous pigmentation along with gastrointestinal manifestations of abdominal pain and anemia suggest the diagnosis of Peutz-Jegher's syndrome.*

**Peutz Jagher's Syndrome**

Peutz-Jaghers syndrome is a rare autosomal dominant, inherited syndrome characterized by mucocutaneous pigmentation and gastrointestinal polyposis.

*Autosomal Dominant Inheritance*$^{Q}$
*Family history often positive*$^{Q}$

| Mucocutaneous Pigmentation | Gastrointestinal Polyposis | Neoplasm's of Non intestinal organs |
|---|---|---|
| • Mucocutancous pigmentation involving lips, buccal mucosa and skin is characteristic (Digits, nails, pains, soles genitalia or any mucosal surface may be involved) | • Hamartomatous polys (Harrison's) Small intestine > Large intestine > Stomach<br>May present with:<br>Intussusception or obstruction (Abdominal pain, bleeding, Anemia)<br>*Although hamartomas are not malignant, a small percentage of patients (13%) may develop malignancies of intestinal organs specially stomach and duodenum* | • Patients with this syndrome have increased risk of developing carcinomas of<br>- Ovary<br>- Breast<br>- Pancreas<br>- Endometrium |

**190. Answer is A (Peutz Jegher's Syndrome) :** *Roxburgh 16th/296*

*Peutz Jegher's Syndrome is a rare autosomal dominant disorder in which perioral and labial pigmented macules, occur in association with jejunal polyps. Presence of malena may reflect polyps in jejunum.*
*Similar complains in sister indicate the hereditary nature of this disorder. Together these features confirm the diagnosis.*
***'Pigmentation'** is not a feature with Gardener's and FAP, nor with villous adenoma.*

**Heriditable (Autosomal dominant) Gastrointestinal polyposis syndromes :**

***Neoplastic polyps***:

***Multiple Adenomalous polyps (Adenomas)*** - are a very common risk factor for colorectal malignancy. Infact if the polyposis is not treated surgically, colorectal cancer will develop in almost all patients (100%), before age 40

**Clues to diagnosis:**

| | |
|---|---|
| Adenomas in large intestine with no associated lesions | **Familial Polyposis coli** |
| Adenomas in large intestine associated with osteomas, fibromas or lipomas | **Gardner's Syndrome** |
| Adenomas in large intestine associated with brain tumors | **Turcot's syndrome** |

***Non-Neoplastic Polyps*:** Peutz Jegher's syndrome and Juvenile polyposis, are two autosomal dominant, heritable conditions, associated with polyps in G.I.T. These polyps are however harmatomas and do not have malignant potential.

**Clues to their diagnosis:**

| | |
|---|---|
| Hamartomatous polyps throughout GIT associated with mucocutaneous pigmentation and tumors of pancreas ovary, breast, lung, uterus. | **Peutz Jeghers Syndrome** *(in small intestine Q > Large intestine Q > Stomach Q)* |
| Hamartomatous polyps throughout GIT associated with various congenital anomalies. | **Juvenile Polyposis** *(in large Intestine Q > small intestine Q > stomach Q)* |

**191. Answer is C (Small bowel) :** *Harrison's 15th / 582 ; CMDT 2009 /576; Harrison 16th/528, 529; Harrison 17th/574, 575 Harrison 18th/p 768, 769, 770*

*Polyps may be seen throughout the gastro intestinal tract but most commonly in the small intestine.*

**Peutz Jegher's syndrome:**

It is an autosomal dominant condition characterized by:

- ***Hamartomatous polyps throughout the gastrointestinal tract, most notably in small intestine Q***
- *Mucocutaneous pigmented macules on the lips, buccal mucosa and skin Q*

| *Syndrome Q* | *Distribution Q* | *Histological type Q* | *Malignant potential Q* | *Associated Q* |
|---|---|---|---|---|
| Peutz Jegher's Syndrome | Small intestine > Large intestine > stomach | Hamartoma | Rare | • Mucocutaneous pigmentation<br>• Tumors of non-intestinal organs<br>- Ovary,<br>- Breast<br>- Pancreas<br>- Endometrium |

*Although hamartomas are not malignant, a small percentage (13%) of patients develop malignancies Q of intestinal organs, specially stomach and duodenum (NOT COLON).*

**192. Answer is B (Peutz Jagher's syndrome):** *Refer previous question*

*Mucocutaneous pigmentation and gastrointestinal manifestations in the form of bleeding (malena) along with a positive family history suggests a diagnosis of Peutz Jagher's syndrome.*

**193. Answer is B (Gardner's Syndrome):** *Quick Reference Handbook for Surgical Pathologists (Springer) 2011/ 111,112*

*Association of epidermoid cysts and bone osteomas in patients with rectal bleeding (gastrointestinal polyposis) is classical of Gardner's Syndrome.*

**Gardner's Syndrome**

ardner's Syndrome is a rare variant of Familial Adenomatous Polyposis (FAP) characterized by the same genetic locus and similar colonic manifestations together several typical ***additional extraintestinal features***

| *Cutaneous* | *Long Bones and Dento Maxillary* | *Ocular* |
|---|---|---|
| ***Multiple Epidermoid Cysts***<br>Multiple Pilomatrixomas<br>**Soft Tissue Tumors**<br>Fibromas (Nuchal Type)<br>Desmoid Tumors<br>Lipomas | ***Osteomas in the mandible, skull or long bones is typical***<br>dontomas<br>nerrupted Teeth<br>upernumary teeth<br>entigerous cysts | ***Congenital Hypertrophy of Retinal Pigment Epithelium(CHRPE)***<br>*(Seen in more than 90 percent of patients and is often bilateral)* |

**194. Answer is B (Stage of lesion) :** *Robbins 7th / 866; Harrison's 17th / 56; Devita's 7th / 1069; Gastrointestinal and Liver diseases by Feldman 8th / 2782*

***The most important prognostic factor of colorectal carcinoma is the 'stage of disease'.***

*The 'stage of disease' gives information related to depth of penetration into bowel wall and extent of regional lymph node spread, both of which are the two most important independent prognostic factors.*

| Most important prognostic factors |
|---|
| *'Extent of Regional Lymph node spread' and 'Depth of tumor invasion' are the most important determinants of prognosis* |

| Single most important prognostic |
|---|
| *Stage of disease*[Q] |

*Stage of disease gives information on both the depth of tumor penetration into the bowel wall and the extent of regional lymph node involvement*

***'Stage' of disease is a superior prognostic factor in comparison to Lymph node status alone***

| Single most important independent prognostic factor |
|---|
| *Lymph node status*[Q] |

*Single most important independent prognostic factor is the Lymph nodal status or the number of positive nodes*

*- Devita 7th / 1069*

*- Gastrointestinal Oncology (2004) / 684*

Pathologic, Molecular and Clinical Features that May Affect Prognosis in Patients with Colorectal Cancer:

| *Feature of Marker* | *Effect of prognosis* |
|---|---|
| **Pathologic** | |
| • Surgical-pathologic stage | |
| Depth of bowel wall penetration | Increased penetration diminishes prognosis |
| Number of regional nodes involved by tumor | 1-4 nodes is better than > 4 nodes |
| • Tumor morphology histology | |
| Degree of differentiation | Well-differentiated is better than poorly differentiated |
| Mucinous (colloid) or signet ring cell histology | Diminishes prognosis |
| Scirrhous histology | Diminishes prognosis |
| • Venous invasion | Diminishes prognosis |
| • Lymphatic invasion | Diminishes prognosis |
| • Perineural invasion | Diminishes prognosis |
| • Local inflammation and immunologic reaction | Improved prognosis |
| • Tumor morphology | Polypoid/exophytic is better than ulcerating/infiltrating |
| • Tumor DNA content | Increased DNA content (aneuploidy) diminishes prognosis |
| • Tumor size | No effect in most studies |
| **Molecular** | |
| • Loss of heterozygosity at chromosome 18q (DCC, DPC4) | Diminishes prognosis |
| • Loss of heterozygosity at chromosome 17q (p53) | Diminishes prognosis |
| • Loss of heterozygosity at chromosome 8p | Diminishes prognosis |
| • Increased labeling index for p21WAF/CIP1 protein | Improved prognosis |
| • Microsatellite instability | Improved prognosis |
| • Mutation in BAX gene | Diminishes prognosis |
| **Clinical** | |
| • Diagnosis in asymptomatic patients | Possibly improved prognosis |
| • Duration of symptoms | No demonstrated effect |
| • Rectal bleeding as a presenting symptom | Improved prognosis |
| • Bowel obstruction | Diminishes prognosis |
| • Bowel perforation | Diminishes prognosis |
| • Tumor location | May be better for colon than for rectum<br>May be better for left colon than for right colon tumors |
| • Age < 30 yr | Diminished prognosis |
| • Preoperative CEA | Diminished prognosis with a high CEA level |
| • Distant metastases | Markedly diminished prognosis |

**195. Answer is A (Resection) :** *Harrison 14th/576; Harrison 17th/578; Harrison 18th/p 774 CMDT 2002 / 665; CMDT 2003/620*

***Patients of colon cancer, with solitary hepatic metastasis without clinical or radiographic evidence of additional tumor involvement should be considered for partial liver resection***, because such procedures are associated with 5-year survival rates of 25-30% when performed on selected individuals by experienced surgeons.

***Resection of isolated (One to three) liver or lung metastasis result in long term survival*** (over 5 years in 20% - 40% of cases) - *CMDT 2002/665*

**196. Answer is A (Surgery) :** *Harrison 18th/p 773, 774 Harrison 17th/578; CMDT 2009/1450-51; Sabiston 16 th/964; CMDT 2003/618-619*

*The presence of metastatic disease to the liver does not preclude the surgical excision of the primary tumor and even the liver metastasis.*

**Treatment of metastatic disease: *presence of isolated metastasis to lung or liver, 1 to 3 in number is not a contraindication to surgery.*** *Treatment here involves resection or cryosurgical ablation of secondries, alongwith the management of the primary.*

The reason for proceeding with surgery for colorectal CA (CRC) in presence of liver metastasis are :

1. First, if the colonic tumor is left untreated, death is imminent, and its cause will not be cancer but colonic obstruction or bleeding.
2. Second, there is a significant cure rate for patients undergoing surgery for CRC metastatic to the liver.

**197. Answer is C (Combined chemotherapy and Radiotherapy) :** *Bailey Love 23rd/1141*

*A combination of chemotherapy and radiotherapy called as 'chemoradiation' is the preferred initial therapy for all anal canal tumors – Bailey*

**198. Answer is A (Lynch Syndrome):** *Multiple references*

*Lynch Syndrome is a genetic diagnosis based on the finding of defective Mismatch Repair (MMR) in the tumor from a germline mutation in one of the Mismatch Repair (MMR) genes.*

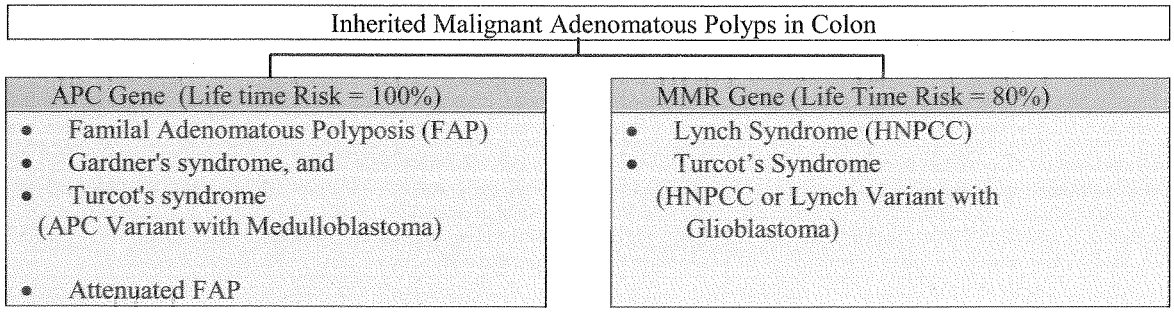
*APC-associated polyposis syndromes include familial adenomatous polyposis (FAP), attenuated FAP, Gardner's syndrome, and Turcot's syndrome. These syndromes are all caused by mutations in the APC gene, located on chromosome 5q.*

FAP is an Autosomal Dominant inherited disorder caused by a mutation in the tumor suppressor gene APC (Adenomatous Polyposis Coli gene).The gene is located on the long arm of chromosome 5 (5q21)

APC-associated polyposis syndromes include

- Familial Adenomatous Polyposis (FAP),
- Attenuated FAP,
- Gardner's syndrome, and
- Turcot's syndrome (May also have a Lynch Syndrome Variant)

*These syndromes are all caused by mutations in the APC gene, located on chromosome 5q.*




**199. Answer is D (Mismatch Genes):** *Multiple references*

*Lynch Syndrome is a genetic diagnosis based on the finding of defective Mismatch Repair (MMR) in the tumor from a germline mutation in one of the Mismatch Repair (MMR) genes.*

**Lynch syndrome (also called hereditary nonpolyposis colorectal cancer)** is an autosomal dominant syndrome characterized by early onset colorectal cancer and increased risk of extracolonic malignancies (in the uterus, ovaries, stomach, urinary tract, small bowell, and bile duct).

Lynch syndrome is a genetic diagnosis based on the finding of defective DNA Mismatch Repair (MMR) in the tumor from a germline mutation in one of the MMR genes. The syndrome has been associated recently with mutations in at least 5 DNA mismatch repair genes (MLH1, MLH2, PMS1, PMS2, and MSH6), which maintain nucleic acid sequence integrity during replication.

HNPCC/Lynch terms are frequently used interchangeably BUT by strict definition HNPCC refers to patients meeting the clinical definition of inherited colorectal carcinoma ("Amsterdam criteria") WHILE, ***Lynch syndrome is reserved only for patients with continued germline mutation in the mismatch repair pathway.***

Not all patients with clinically defined HNPCC will have Lynch syndrome, and not all patients with Lynch syndrome will fulfill the clinical criteria for HNPCC. Lynch syndrome is likely to be a relatively homogenous diagnosis despite the locus heterogenety, whereas HNPCC is more heterogenous and includes both Lynch syndrome and other hereditary genetic causes of HNPCC. The clinical criteria for considering a person to be at risk for Lynch syndrome are the Amsterdam criteria.

Adenomas are believed to precede carcinomas in most instances, and colorectal cancer develops in 75% to 80% of patients with Lynch syndrome, at a median age of 46 years.
It has been reported that for persons with Lynch syndrome, regularly performed colonoscopy with polypectomy can decrease the risk of large bowel adenocarcinoma by approximately 60%.

| Syndrome | Inheritance | Genes | Fetaures |
|---|---|---|---|
| Hereditary nonpolyposis colorectal cancer (HNPCC/Lynch syndrome) | AD | Genes encoding DNA mismatch repair (MMR) proteins<br>*hMLH1 (40%)*<br>*hMLH2 (40%)*<br>*hMSH6 (10%)*<br>*PMS2 and PMS1 (5%)*<br>+<br>EPCAM (5%) | Lynch syndrome-associated tumors:<br>Colorectum (~80% lifetime risk)<br>Endometrium (~60% lifetime risk).<br>Ovary (~12% lifetime risk),<br>Stomach, pancretobiliary, urothelial carcinoma of upper urinary tract (particularly with inverted growth), small bowel, brain, skin (sebaceous adenoma and carcinoma and keratoacanthoma). |

**200. Answer is None (All above genes may be involved) :** *'Gastrointestinal and Liver diseases' by Feldman 8th/2768*
*'Neoplasms of the Colon, Rectum and Anus' 2nd/ 58*

***APC, K-ras and mismatch repair genes are characteristically involved in generation of cancer of colon.***
***β Catenin mutations*** *are uncommon / infrequent mutations seen in a subset of patients who have normal APC. Tumors lacking APC mutations may have activating mutations in β catenin which is the main downstream target of APC action.*

Genes involved in Development of Colorectal Cancer

| Oncogenes / Protooncogenes | Tumor suppressor Genes | Mismatch Repair Genes |
|---|---|---|
| *K – ras* | • *APC*<br>• DCC (Deleted in Ca Colon)<br>• $P^{53}$<br>• SMAD4 (DPC, MADH)<br>• MCC<br>• *TGF – β – RII* | • *h MLH – 1*<br>• *h MSH – 2*<br>• *h MSH – 3*<br>• *h MSH – 6*<br>• *h PMS – 1*<br>• *h PMS - 2* |

**β Catenin Gene Mutations may be seen in a subset of patient who have no mutation in APC.**

- β Catenin is the main downstream target of APC action.
- APC functions to modulate extracellular signals that are transmitted to the nucleus through a cytoskeletal protein 'β catenin' which then regulates transcription and other target genes.
- APC is a tumor suppressor gene that binds to β-catenin and causes its degradation unopposed stimulation of various pathways that lead to tumor genesis.
- ***Besides inactivating mutations of APC gene, tumor genesis can also occur directly through dominant stimulatory mutations of the β-catenin gene. Such mutations are found in 15-20% of Microsattelite Instability colon cancers.***

**Genes altered in sporadic Colorectal Cancer** *(Gastrointestinal and Liver Diseases by Feldman 8th/2768)*

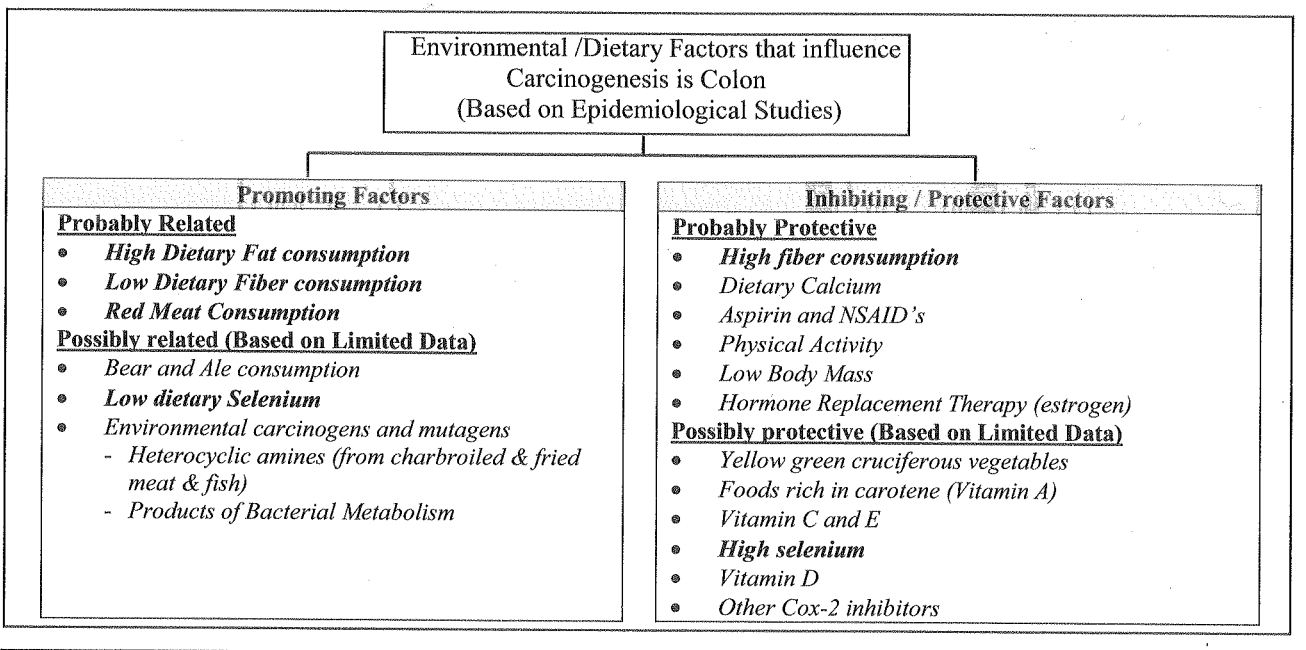
| Gene | Chromosome | Percentage of tumors with Gene Alterations | Gene Class | Gene function |
|---|---|---|---|---|
| ***K-ras*** | 12 | 50 | Proto-oncogene | Encodes guanine nucleotide-binding protein that regulates intracellular signaling |
| ***APC*** | 5 | 70 | Tumor suppressor | ***Regulation of β-catenin that is involved in activation of WnT/TcF signaling*** (activates c-myc, cyclin $D_1$)*; regulation of proliferation and apoptosis; interaction with E-cadherin (cell adhesion?) |
| DCC | 18 | 70 | Tumor suppressor | Netrin-1 receptor; capase substrate in apoptosis; cell adhesion |
| SMAD4 (DPC4, MADH4) | 18 | ? | Tumor suppressor | Nuclear transcriptase factor in transforming growth factor (TGF-β1) signaling; regulation of angiogenesis; regulator of WAF1 promoter; downstream mediator of SMAD2 |
| P53 | 17 | 75 | Tumor suppressor | Transcription factor; regulator of cell cycle progression after cellular stress, of apoptosis, of gene expression, and of DNA repair |
| hMSH2 | 2 | # | ***DNA mismatch repair*** | Maintains fidelity of DNA replication |
| hMLH1 | 3 | # | ***DNA mismatch repair*** | Maintains fidelity of DNA replication |
| hMSH6 | 2 | # | ***DNA mismatch repair*** | Maintains fidelity of DNA replication |
| TGF-β1 RII | 3 | ⊕ | Tumor suppressor | Receptor for signaling in the TGF-β1 pathway; inhibitor of colonic epithelial proliferation, often mutated in tumors with MSI |

*β-Catenin mutations (downstream of APC) are found in 16-25% of MSI colon cancers but not in microsatellite stable (MSS) cancers
#Approximately 15% of sporadic colorectal cancers demonstrate MSI associated with alterations in mismatch repair genes (principally hMSH2 and hMLH1 but also hMSH3, hMSH6, hPMS1, and hPMS2)
⊕ Mutated in 73-90% of MSI colon cancers. Upto 55% MSS colon cancer cell lines may demonstrate a TGF-β signaling blockage distal to TGF-β1 RII.
MSI, nicrosatellite instability; TGF-β, transforming growth factor-β

**201. Answer is A (High fiber diet):** *Gastrointestinal and Liver Diseases by Feldman 8th/2762, Advanced Surgical Practice' by Majid & Kingsnorth (2002)/ 271 , Lange Outline Review' for USMLE STEP 3' by Goldberg 5th / 108*

***Epidemiologic, case control and animal studies suggest that dietary fibers are protective against the development of colon cancer***

**Fat** *is primarily related as a 'promoting' agent* such that high fat in diet is believed to promote carcinogenesis.
*Low Fat has not been shown to have a 'protective' role in carcinogenesis* although it may reduce the incidence of colonic carcinoma indirectly by reducing a 'promoting effect'.
**Low selenium** *is 'possibly related' as a promoting agent*
**Low Protein** has *not been mentioned in relation to carcinogenesis in the colon.*




## Pancreatic Disorders

### Pancreatitis

**202. Answer is C (Hemochromatosis) :** *Harrison 15th / 1793; Harrison 16th/1896;Harrison 17th/2007 Harrison 18th/p 2635*

*Gall stones$^{Q}$, Alcohol ingestion$^{Q}$ and Hypercalcemia$^{Q}$ (e.g. Hypoparathyroidism) have all been mentioned as causes of Acute Pancreatitis.*

***Hemochromatosis has not been included*** $^{Q}$ as a cause in this exhaustive list.

**Causes of Acute Pancreatitis:**

| Common Causes | Uncommon causes |
|---|---|
| Gallstones (including microlithiasis)<br>Alcohol (acute and chronic alcoholism)<br>Hypertrigleceridemia<br>Endoscopic retrograde cholangiopancreatography (ERCP),<br>Truama (especially blunt abdominal trauma)<br>Postoperative (abdominal and nonabdominal operations)<br>Drugs (azathioprine, 6-mercaptourine, sulfonamides, estrogens, tetracycline, valproic acid, anti-HIV medications)<br>Sphincter of Oddi dysfunction | Vascular causes and vasculitis<br>Connective tissue disorders<br>Thrombotic thrombocytopenic purpura (TTP)<br>Cancer of the pancreas<br>Hypercalcemia<br>Periampullary diverticulum<br>Pancreas divisum<br>Hereditary pancreatitis<br>Cystic fibrosis<br>Renal failure |
| **Rare causes** | **Causes to consider in patients with recurrent bouts of acute pancreatitis without an obvious etilogy** |
| Infections (mumps, coxasackievirus, cytomegalovirus, echopvirus, parasites)<br>Autoimmune (e.g., Sjogren's syndrome) | Occult disease of the biliary tree or pancreatic ducts<br>Drugs<br>Hypertriglyceridemia<br>Pancreas divisum<br>Pancreatic cancer<br>Sphincter of Oddi dysfunction<br>Cystic fibrosis<br>Idiopathic |

**203. Answer is B (Appendicitis) :** *Harrison 14th/ 1739, 15th/1788, 1795; Harrison 16th/1893; Harrison 17th/2004 (306.2) Harrison 18th/p 2632, (Table: 312.2)*

*Appendicitis alone does not cause increased amylase.*

*Perforated appendix*, may be associated with *increased amylase*.

**Causes of Hyperamylasemia and Hyperamylasuria:**

| Pancreatiti Disease | Non Pancreatic Disorders | Other Abdominal Disorders |
|---|---|---|
| I. Pancreatitis<br>A. Acute<br>B. Chronic : ductal obstruction<br>C. Complications of pancreatitis<br>1. Pancreatic pseudocyst<br>2. Pancreatogenous ascites<br>3. Pancreatic abscess<br>4. Pancreatic necrosis<br>II. Pancreatic trauma<br>III. Pancreatic carcinoma | I. Renal insufficiency<br>II. Salivary gland lesions<br>A. Mumps<br>B. Calculus<br>C. Irradiation sialadenitis<br>D. Maxillofacial surgery<br>III. Tumor hypermamylasemia<br>A. Carcinoma of the lung<br>B. Carcinoma of the esophagus<br>C. Breast carcinoma, ovarian carcinoma<br>IV. Macroamylasemia<br>V. Burns<br>VI. Diabetic ketoacidosis<br>VII. Pregnancy<br>VIII. Renal transplantation<br>IX. Cerebral trauma<br>X. Drugs : morphine | I. Biliary tract disease : cholecystitis, choledocholithiasis<br>II. Intraabdominal disease<br>A. Perforated or penetrating peptic ulcer<br>B. Interstitial obstruction or infarction<br>C. Ruptured ectopic pregnancy<br>D. Peritonitis<br>E. Aortic aneurysm<br>F. Chronic liver disease<br>G. Postoperative hyperamylasemia |

**204. Answer is 'D' (Acute pancreatitis):** *Harrison 16th/1897; Harrison 17th/2002, 2008; Harrison 18th/p 2636 Kumar & Clarke 5th/398*

*'The diagnosis of acute pancreatitis is usually established by detection of an increased level of serum amylase' Harrison 16th*

*'Serum amylase level is the standard laboratory test carried out to confirm the diagnosis of acute pancreatitis'* ***Kumar & Clarke 5th***

| Measurement during first 24 hours of onset of pain | Measeurement late after presentation |
|---|---|
| An elevation of three times the upper limit of normal clinches the diagnosis (provided overt salivary gland disease and gut perforation or infarction are excluded) | After 48-72 hrs even with continuing evidence of pancreatitis, total serum levels tend to return to normal<br>With a late presentation thus, serum amylase levels may give a false negative result. |

Serum amylase level may be increased in acute cholecystitis, but it does not form a criteria for its diagnosis.

***Remember:*** Q

There is no definitive correlation between the severity of pancreatitis and the degree of serum amylase elevation.
An elevated serum lipase Q or trypsin value is more specific / diagnostic of acute pancreatitis than serum amylase – (Lipase is the single best enzyme to measure for acute pancreatitis Q).

**205. Answer is D (Serum amylase > 350 IU) :** *Harrison 14th/1743; Harrison 16th/not elaborated; Harrison 17th/2008 Harrison 18th/p 2636*

*Serum amylase does not form any cirteria for prognosis in acute pancreatitis. (Remember this fact)*
*Therefore, if amylase is present as any of the options, you can easily and safely exclude it.!!*

**Ranson's criteria for prognosis in acute pancreatitis include :** (Adverse factors)

| At the time of Admission | During initial 48 hours |
|---|---|
| 1. *Age > 55 years* Q | 1. *Fall in haematocril > 10%* |
| 2. *Leucocytosis > 16.000/μl* Q | 2. *Fluid deficit > 4000 ml* |
| 3. *Hyperglycemia > 200 mg/dl* | 3. *Hypocalcemia < 8 mg/dl* Q |
| 4. *Serum LDH > 400 IU/L* | 4. *Hypoxemia < 5mg/dl* |
| 5. *Serum AST > 250 IU/L* | 5. *Increased BUN > 5mg/dl* |
| | 6. *Hypoalbuminemia < 3.2 g/dl* |

**206. Answer is A (Serum Amylase) :** *Harrison 16th / 1897; 14th / 1743; Harrison 17th/2008; Harrison 18th/2636, 2637*

*Serum Amylase does not form any criteria for prognosis in Acute Pancreatitis.*
***Although elevated serum amylase level is important for establishing diagnosis of acute pancreatitis, it plays no role in predicting prognosis or severity.***

*"There appears to be no definite correlation between severity of pancreatitis and the degree of serum amylase elevation. After 48 to 72 hours, even with continuing evidence of pancreatitis, total serum amylase levels tend to return to normal." - Harrison*

***Hyperglycemia (Glucose), Hypocalcemia (Calcium) and elevated serum AST are all poor prognostic factors in accordance with Ranson's criteria as elaborated in the previous question.***

**207. Answer is D (Prothrombin Time > 2 sec):** *Harrison 14th/1743*

*Prothrombin time is not included as an index in Ranson's criteria.*
*It is the single best answer of choice.*
*TLC > 16,000, Calcium < 8 mmol/l, Hyperglycemia > 200 mg/dl are all poor prognostic signs for acute pancreatitis in accordance with Ranson's criteria.*

**208. Answer is D (Hyperamylasemia):** *Refer previous question*

*Serum amylase levels do not form any criteria for prognosis in acute pancreatitis.*
*Hyperglycemia, Hypocalcemia and raised LDH levels are poor prognostic factors according to Ranson's criteria.*

**209. Answer is A (Low serum Lipase):** *Harrison 18th/p 2636, 2637 Harrison 17th/2008*

*The presence of sudden onset epigastric pain that radiates to the back in an alcoholic patient suggests the diagnosis of Acute Pancreatitis.*
*Acute pancreatitis is characterized by an elevated serum lipase leve and not a low serum lipase*
*'An elevated serum lipase is more specific for pancreatitis than a serum amylase level'- Harrison*

**210. Answer is B (Serum Lipase):** *Harrison 18th/p 2636, 2637 Harrisons 17th/2008*

*Serum lipase elevation is the most specific laboratory test for establishing a diagnosis of Acute Pancreatitis*
*'A three fold elevated serum lipase value is usually diagnostic of acute pancreatitis' – Harrison*

*Serum Lipase levels and serum amylase levels are both used to establish the diagnosis of acute pancreatitis*

*An elevated serum Lipase level is more specific for pancreatitis than a serum amylase level because many other pathologic conditions may present with an elevated amylase level. Serum lipase is therefore the single best answer of choice.*

**211. Answer is B (Serum lipase) :** *Harrison 18th/p 2636, 2637 Harrison's 17th/2008*

*Serum lipase elevation is the most specific laboratory test for establishing a diagnosis of Acute Pancreatitis*
*'A three fold elevated serum lipase value is usually diagnostic of acute pancreatitis' – Harrison*

*Serum Lipase levels and serum amylase levels are both used to establish the diagnosis of acute pancreatitis*

*An elevated serum Lipase level is more specific for pancreatitis than a serum amylase level because many other pathologic conditions may present with an elevated amylase level. Serum lipase is therefore the single best answer of choice.*

**212. Answer is A (Purtscher's retinopathy) :** *Harrison 18th/p 2642 Harrison's 16th/1898; 15th / 1796*

*Purtscher's retinopathy is a relatively unusual complication of acute pancreatitis*. It is manifested by ***sudden and severe loss of vision***. It is believed to be due to occlusion of the posterior retinal artery with aggregated granulocytes.

**Peculiar Fundoscopic appearance :**

*Cotton wool spots and hemorrhages confined to an area limited by the optic disk and macula.*

**213. Answer is A (Purtscher's retinopathy) :** *Harrison's 15th / 1796; Harrison 16th/1898/ Harrison 17th/2009*

*Purtscher's retinopathy is a relatively unusual complication of acute pancreatitis*. It is manifested by *sudden and severe loss of vision*. It is believed to be due to occlusion of the posterior retinal artery with aggregated granulocytes.

**Peculiar Fundoscopic appearance :**

Cotton wool spots and hemorrhages confined to an area limited by the optic disk and macula.

**214. Answer is B (Gall stone pancreatitis):** *Oxford textbooks of surgery 2nd/1766*

*The prognosis is best in patient where pancreatitis is caused by a remediable cause such as cholelithiasis. 'Eradication of gall stone disease' prevents further attacks of pancreatitis. -Oxford text.*

The etiological mechanism probably involves the transient obstruction of pancreatic duct by a gall stone in the common bile duct at the Ampulla of Vater.

*Good prognosis is also evidenced by the fact that gall stones are recoverable in the faeces of over 90% of patients within 10 days of an attack, suggesting that the obstruction is brief and that most such stones pass into the duodenum.*

**215. Answer is C (Calcium) :** *Harrison 16th/1899; 17th/2009, 2010; Harrison 18th/p 2640, 2641 C.M.D.T. 2009/626; Kumar & Clark 5th/399*

*'Calcium gluconate must be given intravenously if there is evidence of hypocalcemia with tetany'- CMDT 2009/626*

| **Drugs evaluated by prospective controlled trials but found ineffective** – *H/16th/ 1899* | **Drugs with some beneficial role** |
|---|---|
| Glucagon<br>H2 blockers<br>Protease inhibitors like Aprotinin<br>Glucocorticoids<br>Calcitonin<br>NSAIDS<br>Lexiplafant (platelet activating factor inhibitor) | Analgesic for pain (Harrison)<br>Prophylactic anititbiotics (Harrison)<br>Calcium gluconate (hypocalcemia or tetany) CMDT<br>Octreotide (Harrison) : Reduced mortality but no change in complication<br>Gabexale (Harrison) : No affect on mortality but reduced pancreatic damage. |

| Treatment of acute pancreatitis |
|---|
| • Analgesia for pain (Mepridine)<br>• IV fluid and colloids : to maintain normal intravascular volume<br>• No oral alimentation<br>• Nasogastric suction: to decrease gastrin release from stomach and prevent gastric contents from entering duodenum.<br>• Prophylactic antibiotics<br>• Feeding : Entral nutrition by nasojejunal tube |

**216. Answer is B (Pseudocyst) :** *Harrison 18th/p 2642 Harrison 17th/2011; Schwartz 7th/704*

*"**Pseudocyst** is the most common complication, usually occurring after 2-3 weeks" - Schwartz Handook, 7th/704*

**217. Answer is B (Pancreatitis) :** *Harrison 17th/2008, 2009, 2011 Harrison 18th/p 2642, 2643*

*Most common cause of pancreatic pseudocyst is Pancreatitis (90%).*

*The second most common cause is trauma (10%).*

**218. Answer is D (Mostly present in head of pancreas):** *CSDT 11th/635, 638, Schwartz 7th/1256, 1257; Harrison 14th/1747; 15th/1795; 16th/1901*

*Short bowel syndrome (massive small bowel resection) is associated with Hypergastrinemia.*

*Most common site for pseudopancreatic cyst is the body and tail of pancreas - Harrison*

**Pseudopancreatic cyst** (called 'pseudo' because they do not have an epithelial lining)

| **Etiology :** | **Site :** | **Diagnosis:** |
|---|---|---|
| *Pancreatitis (90%) (most common)* Q<br>*Trauma (10%)* Q | ***85% are seen in body and tail***<br>*15% are seen in head* | *- Serum amylase level is elevated* Q<br>*- Sonography is the investigation of choice* Q<br>*- X-Ray : Pseudocysts may be localized, displacing some portion of git.* Q |
| **Complications :** | **Factors indicating possibility of hemorrhage** | |
| Pain due to expansion<br>*Haemorrhage*<br>*Rupture*<br>Abscess | Increase in size<br>*Localized brui over mass* Q<br>*Sudden decrease in Hb or hematocrit* Q | |

**Management**

- *Pseudocyst > 5cm diameter is an indications for drainage* Q
- Pseudocyst *less than 5 cm* in diameter and *less than 6 weeks old should be observed* Q, as they tend to resolve spontaneously
- *Initial management : US/CT guided, single or repeated needle aspirations*
- Later : patients who do not respond to above modality are treated with surgical therapy preferred modality : *Internal drainage of cyst by cystojejunostomy.* Q

**219. Answer is A (Percutaneous aspiration is treatment of choice):** *Harrison 14th/1747,15th/1795;16th/1901, 1902; 17th/2011, 2348; Harrison 18th/p 2642 CSDT 11th/ 635, 638, Schwartz 1256, 1257*

*Percutaneous aspiration has emerged as a simple and frequently used initial procedure in the management of uncomplicated persistant pancreatic pseudocysts.* However *it cannot be termed as the treatment of choice. Surgical internal drainage in the form of cystojejunostomy continues to be the treatment of choice.*

**Treatment of Pancreatic Psuedocyst:**

| ***If the Pseudocyst is shrinking, & in stable patients who are free of complications*** | ***If the pseudocyst is expanding, or not responding to above treatment, or is complicated by rupture, hemorrhage or abscess formation.*** |
|---|---|
| Conservative treatment is indicated.*<br>Alternatively, a USG / CT guided single or repeated needle aspiration can be done. | Operative treatment is indicative<br>Either external or preferably internal drainage of the cyst can be done |

***A singnificant number of pseudocyst will resovle sponteaneously more than 6 weeks after their formations*** Q

| ***Indications for Drainage :*** |
|---|
| *1. Pseudocyst > 5cm in diameter.* Q |
| *2. Persisting for > 6 weeks.* Q |

## Endocrinal Tumors of Pancreas

**220. Answer is none or D (None or ACTH):** *Harrison 18th/p 3057 Harrison's 17th/2348*

*VIP, Insulin Somatostatin and ACTH may all be secreted from pancreatic endocrine tumors. Amongst the options provided ACTH is the most rare peptide associated with Pancreatic Endocrine Tumors, and hence may be selected as the single best answer of exclusion.*

| Insulin > VIP > Somatostatin (Rare) > ACTH (Rare) |
|---|

| Name | Biologically active Peptides secreted | (New Cases/$10^6$ Population/ Year) | Tumour location |
|---|---|---|---|
| Zollinger Ellison Syndrome | Gastrin | 0.5-1.5 | Duodenum (70%)<br>Pancreas (25%) |
| VIPoma (Verner Morrison Syndrome, Pancreatic cholera, WDHA) | VIP | 0.05 – 0.2 | Pancreas (90% in adult) |
| Glucagonoma | Glucagon | 0.01 – 0.1 | Pancreas (100%) |
| Insulinoma | Insulin | 1 – 2 | Pancreas (> 99%) |
| Somatostatinoma | Somatostatin | Rare | Pancreas (55%)<br>Duodenum-Jejunum (44%) |
| GRFoma | Growth hormone releasing hormone | Unknown | Pancreas (30%)<br>Lung (54%) |
| ACTHoma | ACTH | Rare | Pancreas |

**221. Answer is D (Massive HCl in response to histamine injection) :** *Harrison 15th/1661, Harrison 16th/1894; 17th/1868 Harrison 18th/p 2455*

*Massive secretion of HCl is seen in response to stimulation with Secretin (not with Histamine).*

Zollinger Ellison Syndrome (as mentioned in the previous question) is characterized by unregulated secretion of gastrin leading to hypersecretion of gastric acid and the resulting manifestations. The most common presentation is with :

| | |
|---|---|
| **Peptic ulceration** Q : | • ***Most common manifestation***, occuring in 90% of patient<br>• ***Most common site is duodenum (duodenal bulb)***<br>• **Clinical situations that raise special suspicion include :**<br>a. *Ulcers beyond the duodenal bulb (second part of duodenum and beyond) because these are unusual locations for ulcers in Peptic ulcer diseases.* Q<br>b. *Ulcers refractory to standard medical therapy* Q<br>c. ***Ulcers are recurrent*** Q<br>d. *Ulcers presenting with frank complications.* Q |
| **Diarrhea** Q : | ***Is the most common manifestation*** Q<br>Etiology is multifactorial, and it may have a secretory component as well. |

***Gastrin provocative tests*** *are used when acid secretory studies are not contributory* and include :

1. *Secretin stimulation test* Q *: most sensitive and specific* Q
2. Calcium infusion test
3. Standard meal test

***Histamine stimulation is not used and it does not bring about massive release of HCl in such patients.***

**222. Answer is A (Peptic Ulceration, Gastric Hypersecretion, Non β Cell Tumour) :** *Harrison 16th/ 2227; 17th/1868 Harrison 18th/p 2455*

*Zollinger Ellison Syndrome is characterised by peptic ulceration due to gastrin hyper secretion by a non beta cell tumor.*

**Zollinger Ellison Syndrome**

**'Gastrinomas' ( non β cell tumour)** Q
↓
**Increased gastrin** Q **secretion**
↓
**Gastric acid hypersecretion** Q
↓
**Peptic ulceration** Q

**223. Answer is D (Decreased ratio of BAO to MAO):** *Harrison 15th/1661; 16th/2227; 17th/1868; 18th/p 2455, 2456*

*Zollinger Elision syndrome is characterized by an increased basal gastric acid output. The ratio of BAO to MAO (maximal acid output) is increased.*

| Presenting symptom in order of frequency |
|---|
| • Abdominal pain (70-100%) |
| • Diarrhea (37-73%) |
| • Gastroesophageal reflux disease (GERD) (30-35 years) |

*10-20% of patients present with diarrhea only.*

| Observation that should suggest the diagnosis |
|---|
| • Peptic ulcer disease (PUD) with diarrhea |
| • PUD in an unusual location or with multiple lesions |
| • PUD that is refractory to treatment or persistent |
| • PUD that is associated with findings suggestive of MEN I |
| • PUD without H. pylori infection. |

*Chronic unexplained diarrhea should also suggest gastrinoma.*

**Diagnosis of Zollinger Ellison Syndrome**

| | | |
|---|---|---|
| STEP I | Assess fasting gastrin level | Gastrin levels are increased |
| STEP II | Assess acid secretion : BAO estimation | BAO is increased ; BAO / MAO is increased |
| STEP III | Perform provocative test if required. | i.v. secretin induces substantial increase in serum gastrin. |

**224. Answer is C (Gastrin):** *Harrison 18th/3057; Harrison 16th/ 2227; 17th/1868 Harrison 18th/p 2455*

*Zollinger Ellison Syndrome is characterised by peptic ulceration hypersecretion of gastrin by a non-beta cell tumor. Zollinger Ellison Syndrome is synonymous with Gastrinomas*

**225. Answer is B (Secretin injection test) :** *Harrison 14th/1614, 15th/1662; 16th/2227, 1891, 1894; 17th/1868 Harrison 18th/p 2455, 2456*

*Secretin injection test is the most valuable provocative test in identifying patients with ZES.*

**Secretin injection test :**

- In normal individuals, and patients with common Duodenal ulcer, secretin produces either no change or a small reduction or increase in serum gastrin levels. However, in ZES patients i.v. secretin induces substantial increase in serum gastrin.
- Otherwise however remember that the diagnosis of 'Gastrinoma' in a patient with clinical features consistant with ZES depends on demonstration of increased serum gastrin levels.

**$Ca^{++}$ infusion test & 'Standard Test Meal' tests** are the other 2 provocative tests. They are not as valuable as sercretin test.

**ACTH stimulation test** is used for diagnosis of Addison's disease for which it is the only reliable test.

**226. Answer is B (Secretin injection test):** Repeat; *Harrison 17th/1868 Harrison 18th/p 2455, 2456*

*Gastrinomas (Zollinger Ellison Syndrome) are characterized by peptic ulceration due to hypersecretion of gastrin by a non-beta cell tumor. Secretin injection test is the most valuable provocative test in identifying patients with ZES.*

**227. Answer is B (Omeprazole):** *Harrison 15/1662; 16th/2227; 17th/1869 Harrison 18th/p 2456*

*The gastric acid hypersecretion in patients with gastrinomas can be controlled in almost every case by oral gastric antisecretory drugs. Because of their long duration of action potency, allowing once or twice a day dosing, the proton pump inhibitors are the drug of choice - Harrison*

**228. Answer is A (PPI):** *Harrison 16th / 1759; 17th/1869 Harrison 18th/p 2456*

*PPIs are the treatment of choice for Zollinger - Ellison Syndrome and have decreased the need for total gastrectomy.*
*- Harrison 16th / 1759*

**229. Answer is A ('72 hour' fast test):** *Harrison 18th/p 3066, 3067 Harrison's 17th/2354, 2355, Oxford Textbook of Medicine 4th/365, 366, 'Clinical Endocrinology' by Grossmann 2nd/534*

***The Gold standard test for diagnosis of Insulinoma is a supervised '72 hour fast' test***
*Diagnosis of Insulinoma requires demonstration of inappropriately high levels of plasma Insulin ( and C- peptide) in the presence of documented hypoglycemia (Achieved by 72 hour fast test).*

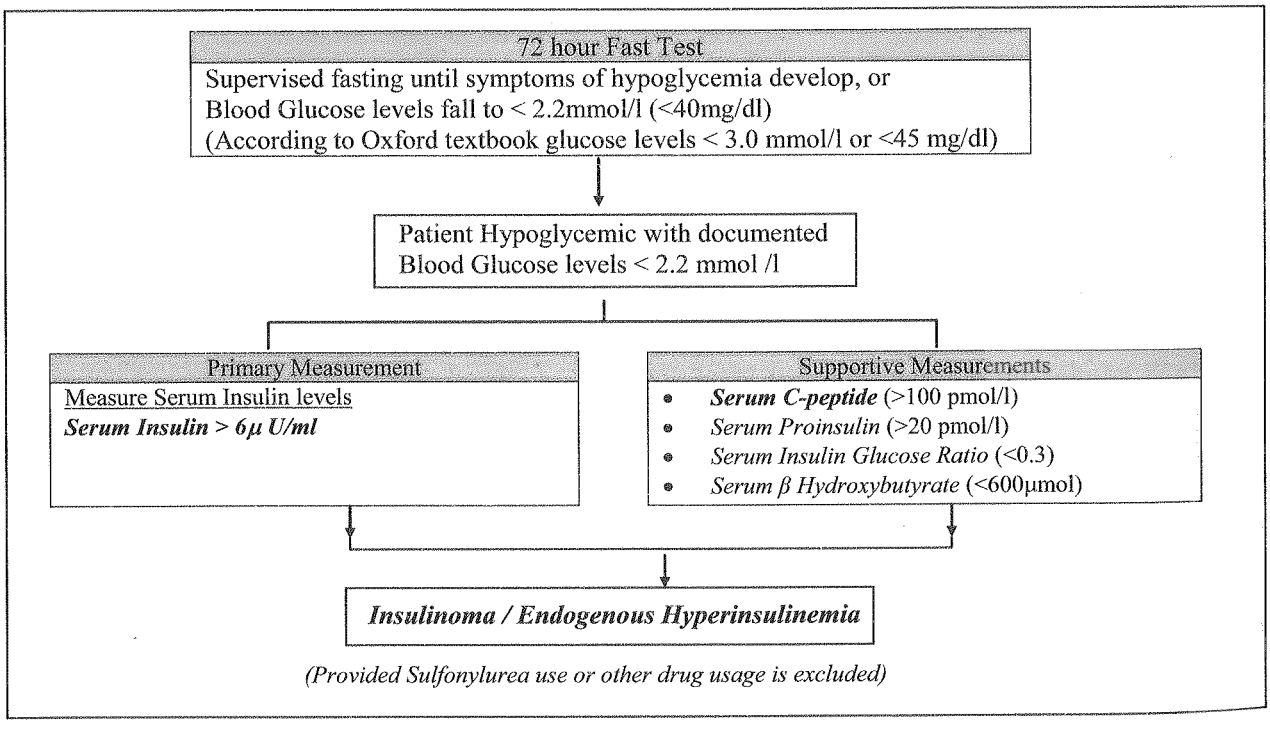
*Absolute values of Insulin or C- peptide are not reliable in establishing a diagnosis unless hypoglycemia is documented*

***The '72 hour fast test' allows demonstration of hypoglycemia, together will elevated levels of Insulin and C-peptide and thus becomes the most reliable – gold standard test for establishing a diagnosis of Insulinoma***

**Diagnosis of Insulinoma: '72 hour fast' test**

- The diagnosis of Insulinoma requires the demonstration of an inappropriately elevated plasma insulin (and C-peptide) at the time of hypoglycemia
- The '72 hour fast' test involves supervised fasting for upto 72 hours or until hypoglycemia can be documented (<2.2 mmol/L or < 40 mg/dl)
- The test is considered positive if at any time when blood glucose levels drop to < 2.2mmol/l (40 mg/dl), the serum insulin levels are recorded to be greater than 6μU/ml. (and C- peptide levels > 100 pmol/l)
- *Studies indicate that 100% of patient with insulinoma will be detected after a supervised 72 hour fast and hence this test is considered the gold standard test*

| | |
|---|---|
| *First 24 hours :* | *70-80% of patients with insulinoma can be detected* |
| *Upto 48 hours :* | *98% of patients with insulinoma can be detected* |
| *By 72 hours:* | *100% of patients with insulinoma can be detected* |



**230. Answer is C (Usually multiple):** *Harrison 18th/p 3066 Harrison's 17th/2354*

*Insulinomas are usually single and not multiple (>90%) – Harrison's*

*Insulinomas are endocrine tumors of pancreas derived from Beta cells.*
*They are generally small (>90% < 2 cm), usually not multiple (90%) and only 5-15% are malignant (usually benign).*
*– Harrison's*

**Insulinomas**

Insulinomas are Endocrine tumors of the pancreas derived from Beta cells that ectopically secrete Insulin and result in Hypoglycemia

Average age of occurrence is 40-50 years

- *Generally Small* Q (>90% are < 2cm)
- *Usually single* Q (Not multiple in 90%)
- *Usually Benign* Q (5-15% are malignant)
- *Invariably occur in the pancreas* Q (Distributed equally in pancreatic Head, Body and Tail)

**Symptoms due to Hypoglycemia**

Most common symptoms are due to the effect of hypoglycemia on the central nervous system (Neuroglycemic Symptoms)

- Confusion
- Headache
- Disorientation
- Visual difficulties
- Irrational behavior (even coma)

**Symptoms due to Excessive Catecholamine Release secondary to Hypoglycemia**

- *Sweating*
- *Tremor*
- *Palpitation*

**231. Answer is A (Present in Pancreas):** *Harrison 18th/p 3066 Harrison's 17th/2534*

*The most common site of Insulinomas is the Pancreas.*

**232. Answer is D (Insulinoma)** : *Harrison 14th/ 245; Harrison 15th/ 251; 16th/ 2227; 17th/2354 Harrison 18th/p 3066*

*Insulinoma is characterised by an increase in weight (weight gain) and not by weight loss.*

***Weight gain may result from increased food ingested to combat symptoms of hypoglycemia.***

Classic presentation of ***insulinoma*** : ***'Whipple's triad'*** Q : - *Harrison 14th/589*

1. *Fasting hypoglycemia* Q
2. *Symptoms of hypoglycemia* Q
3. *Immediate relief after I.V. glucose administration* Q

**233. Answer is B (Rectum is sapred):** *Harrison 17th/2350, 2351; Sleisenger and Fordtran's Gastrointestinal & Liver diseases 8th/609; SEER National Registry Database Official Publication.*

***Rectum is not spared from carcinoids.***

*'Rectum is a common site of carcinoids (19% of all carcinoids) and the incidence appears to be rising'*
*– Sleisenger and Fordtran's 8th/609*

**Rectum is a common site of carcinoid tumors (It is not spared)**

*Rectum is a common site of carcinoid tumors in the gastrointestinal tract accounting for almost 19% of all carcinoid tumors of the GI tract in the late SEER registry (1992-1999).*
*It is the second most frequent site of Carcinoids after the ileum in accordance with the Pan SEER registry (1973-1999).*

| Carcinoid site | Early SEER (1973-1991) | Late SEER (1992-1999) | Pan SEER (1973-1999) |
|---|---|---|---|
| Gastrointestinal tract | 61.57 | 67.55 | 64.31 |
| Esophagus | 0.05 | 0.06 | 0.06 |
| Stomach | 3.55 | 5.85 | 4.61 |
| Small intestine | 28.82 | 28.22 | 28.54 |
| Duodenum | 1.94 | 3.83 | 2.80 |
| Jejunum | 2.11 | 1.48 | 1.81 |
| Ileum | 16.23 | 13.35 | 14.92 |
| Not specified | 7.86 | 8.74 | 8.26 |
| Colon | 9.48 | 7.62 | 8.62 |
| Appendix | 6.76 | 2.43 | 4.77 |
| Rectum | 9.44 | 18.54 | 13.61 |

**Small intestine and appendix account for almost 60% of gastrointestinal carcinoids**

Small intestine and appendix together account for about 58% (≈60%) of gastrointestinal carcinoids according to the data from early SEER (1973-1991) and for about 51% of gastrointestinal carcinoids from the Pan SEER data (1973-1999)

*Although the statement (option A) is not entirely correct in view of the late SEER registry and/or the Pan SEER data, this may be accepted as a 'true statement' for the purpose of the question.*

**Site Specific incidence rate of Carcinoid Tumors**

*The reported anatomic distribution of carcinoid tumors varies widely amongst different textbooks depending on the source of data quoted.*
*Several textbooks including Schwartz and Sabiston, continue to mention Appendix as the most common site of gastrointestinal carcinoids however these incidence rates are based on old data before the 1970's and most studies thereafter report other locations as being more frequent. Results from Surveillance, Epidemiology and End Results (SEER) natural registry are now accepted as standard (Harrison.)*

**Five year survival is > 60%.**

*The five survival for all gstrointestinal carcinoids is getaer than 60 percent*

| 5 Year Survival | Early SEER | Late SEER | Pan SEER |
|---|---|---|---|
| All Gastrointestinol Carcinoids | ≈57% | ≈68% | ≈62.5% |

**Appendecial carcinoids are more common in females**

*'Appendecial carcinoids are more coomon in females. Two of Three cases of appendecial carcinoids are females.' - Sleisenger & Fordtradn 8th/609*

***The evaluation of carcinoid tumors by Pan-SEER (1973-1999) reveals a slight overall female predominance in all type of carcinoid tumors (55%).***

Male and Female Distribution (Pan-SEER – 1993-1999)

| Female > Males | Males > Females | Male ≈ Females |
|---|---|---|
| • *Stomach* | • *Esophagus* | • *Small Intestines* |
| • *Colon* | | • *Rectum* |
| • *Appendix* | | |

**234. Answer is B (Secretory Diarrhoea):** *Harrison 18th / 3068*

***The principle feature of VIPOMA is large volume secretory Diarrhoea.***
*Diarrhoea is secretory in nature, persists during fasting and is almost always greater than >1Litre per day (>3 Litres per day in 70 percent). A stool volume less than 700 ml per day is proposed to exclude the diagnosis. Most patients do not have accompanying Steatorrhea.*

**VIPOMAS** *(Verner-Morrison Syndrome/ Pancreatic Cholera/WDHA Syndrome)*
*VIPomas are tumours that secrete large amounts of Vasoactive Intestinal Peptide (VIP)*
*VIP is an important neurotransmitter ubiquitously present in the CNS and GI T*

- The most common location of VIPomas is the Pancreas
- Most common site within the pancreas is the pancreatic tail
- Usually Solitary
- Usually Malignant (37-68 % have hepatic metastasis at diagnosis

**VIP**
*Stimulates Small Intestinal chloride secretion*
*Stimulates smooth muscle contractility*
*Inhibits acid secretion*
*Has vasodilatory effects*

Typical Features (**WDHA**)

Watery Diarrhoea (Large Volume Secretory Diarrhoea leading to dehydration)
Hypokalemia (Diarrhoea severe enough to cause hypokalemia)
Achlorhydria (Hypochlorhydria from increased small intestinal chloride secretion)

*The principle Symptoms are large volume diarrhoea (100 %) severe enough to cause hypokalemia (80-100%), dehydration (83%), hypochlorhydria (54-76%) and **flushing (20%)***

*Most patients do not have accompanying Steatorrhea*

Other Features

- Increased stool Volume due to increased secretion of sodium and potassium which with the anion account for osmolality of the stool
- Hyperglycemia (25-50%
- Hypercalcemia (25-50%)

*The diagnosis requires demonstration of an elevated plasma VIP level and the presence of large volume secretory diarrhea.*

**235. Answer is D (Hypocalcemia):** *Harrison 14th / 1752 ; 15th / 1803; 16th/2228, 2229; 17th/2355, 2356 Harrison 18th/p 3061, 3062*

**Pancreatic cholera is a Pancreatic endocrine tumor, most commonly of the Delta cells, characterized by net secretion of salt and water by gut:**

| Features of Pancreatic cholera : |
|---|
| - *Severe watery diarrhea* Q / flushing / weight loss |
| - ***Hypokalemia*** Q |
| - ***Hypochlorhydria*** Q |
| - ***Hypercalcemia*** Q ***(not Hypocalcemia)*** |
| - ***Hyperglycemia*** Q |
| - Inordinate fecal water and electrolyte loss |

Pancreatic cholera is synonymous with 'Verner – Morrison Syndrome' or 'WDHA Syndrome'

| WDHA Syndrome |
|---|
| Watery diarrhea |
| Hypokalemia |
| Achlorhydria |

**Pancreatic cholera** results from excessive secretion of VIP from endocrine tumors i.e. VIPomas
'VIP' is an important neurotransmitter ubiquitously present in CNS and G.I. tract
Known actions of VIP explain most features of the clinical syndrome. These include :

- stimulation of small intestinal chloride secretion
- effects on smooth muscle contractility
- inhibition of acid secretion
- vasodilatory effects

**236. Answer is C (Median Survival in locally advanced (stage III) disease is 3- 6 months) :** *Integrated Medical and Surgical Gastroenterology (2004) / 206; Internal Medicine: Just the facts (MCG raw Hill) (2008) / 474; other References along with text*

***Median survival of locally advanced (Stage III) disease is 6-10 months and not 3-6 months. Median survival of 3-6 months is a feature of Metastatic Stage IV disease.***

**Median survival in locally advanced disease (stage III) is 6 – 10 months**

Metastatic disease (stage IV) is associated with a median survival of 3 – 6 months.
Stage III locally advanced disease is associated with a median survival of 6 – 10 months

| Clinical / Radiological Criteria | Median Survival |
|---|---|
| • Resectable Disease (Stage I and Stage II) | 15 – 20 months |
| • Locally Advanced Disease (Stage III) | 6 – 10 months |
| • Metastatic Disease (Stage IV) | 3 – 6 months |

**$p^{53}$ mutation is seen in 75% of cases of Pancreatic cancer**

| Gene | Pancreatic Cancer% | Colorectal Cancer (%) |
|---|---|---|
| • P16 | 95 | 0 |
| • K – ras | 90 | 50 |
| • ***P53*** | ***75*** | ***60*** |
| • DPC4 | 55 | 15 |
| • BRCA 2 | 7 | ? |

*Taken from Gastrointestinal and Liver disease' by Feldman 8th /1312*

**Hereditary Pancreatitis significantly increases the risk of Pancreatic Cancer**

*'One of the most important genetic factors in pancreatic carcinoma is hereditary pancreatitis. Affected patients have an abnormal trypsin gene that is transmitted as an autosomal dominant trait. Their risk of development of pancreatic cancer by age 70 years is estimated at 40%' - 'Gastrointestinal and Liver Diseases' by Feldman 8th / 1309*

**Five Year Survival after curative Pancreaticoduodenectomy approaches 15 -20%.**

- *Overall 5-year survival rate with pancreatic cancer is 5%*
- *5 – year survival rate for patients undergoing curative tumor resection (pancreaticoduodenectomy) is 15% - 20%*

**Note**

*Only 10% of pancreatic cancers are diagnosed at on early stage when radical resection with curative intent can be performed. - 'Pathophysiology of Disease (Lange) 5th /454'*

## Cystic Fibrosis

**237. Answer is B (Abnormality in CFTR leads to defective Calcium Transport):** *Harrison 18th/p 2147 Harrison's 17th/1632; Robbins 7th/494; Nelson's 18th ;Board Review Series 'Paediatrics' 2nd/272*

***The genetic defect in cystic fibrosis produces an abnormal Cystic fibrosis Transmembrane Regulator protein (CFTR protein). This abnormal CFTR protein is associated with defective $Na^+$ and $Cl^-$ transport and not defective calcium transport***

**Cystic fibrosis is an autosomal recessive disorder with an abnormal CFTR protein that leads to defective transport of $Na^+$ and $Cl^-$**

- Cystic fibrosis is a monogenic disorder with *autosomal recessive (AR) inheritance*
- CF results from a mutation in the gene that encodes *for CF transmembrane receptor protein (CFTR)*
- The genetic mutation is located on *chromosome 7Q*
- The defective CFTR protein causes *dysfunction in transport of sodium and chloride (Na+ & cl-) in epithelial cells*

**Cystic fibrosis predisposes to pulmonary infection with Pseudomonas**

- *Cystic fibrosis airways are predisposed to chronic infections with staphylococcus and pseudomonas due to failure to clear thick viscid mucus*

| Charachteristic sputum microbiology in CF patients |
|---|
| First organisms to be recovered are Hemophillus influenzae & staphylococcus aureces. |
| Thereafter Pseudomonas Aeruginosa is cultured from lower respiratory tract |
| Burkholderia (formerly Pseudomonas cepacia) is also recovered from CF sputum and is considered pathognomic |

**Cystic fibrosis may lead to cirrhosis**

- *Significant liver disease occurs late in the natural history of CF*
- *Biliary Cirrhosis and multilobular cirrhosis are established complications*

**Clinical Features and Diagnostic Criteria for Cystic Fibrosis:Review**

| **Chronic Sinopulmonary disease manifested by** |
|---|
| 1. Persistent colonization/infection with typical cystic fibrosis pathogens, including Staphylococcus aureus, nontypeable, Hemophilus influenzae, ***mucoid and nonmucoid Pseudomonas aeruginosa***, Burkholderia cepase |
| 2. Chronic cough and sputum production |
| 3. Persistent chest radiograph abnormalities (eg. Bronchiectasis, atelectasis, infiltrates, hyperinflation) |
| 4. Airway obstruction manifested by wheezing and air trapping |
| 5. Nasal polyps; radiographic or computed tomographic abnormalities of paranasal sinuses |
| 6. Digital clubbing |
| **Gastrointestinal and nutritional abnormalities, including** |
| 1. Intestinal: meconium ileus, distal intestinal obstruction syndrome, rectal prolapse |
| 2. Pancreatic: pancreatic insufficiency; recurrent pancreatitis |
| 3. Hepatic: chronic hepatic disease manifested by clinical or histologic evidence of focal biliary ***cirrhosis***, or multilobular ***cirrhosis*** |
| 4. Nutritional: failure to thrive (protein-calorie malnutrition), hypoproteinemia, edema, complications secondary to fat-soluble vitamin deficiency |
| **Metabolic Abnormalities** |
| 1. Salt depletion syndrome |
| 2. Hyponatremia |
| 3. Hypochloremia |
| 4. Hypokalemic metabolic Alkalosis |
| **Male urogenital abnormalities resulting in obstructive azoospermia (congenital bilateral absence of vas deferens)** |

**238. Answer is B (Demonstrate an abnormal nasal potential difference):** *Nelson's 18th/1808; Harrison 18th/p 2149 Harrison's 17th/1634; Rudolph's Pediatrics 21st/1972*

***Nasal Potential Difference is a sensitive test of electrolyte transport (CFTR function) that can be used to support or refute a diagnosis of cystic fibrosis when sweat chloride levels are normal or border line and two CF mutations cannot be demonstrated by DNA testing.***

**Diagnostic criteria for cystic fibrosis**

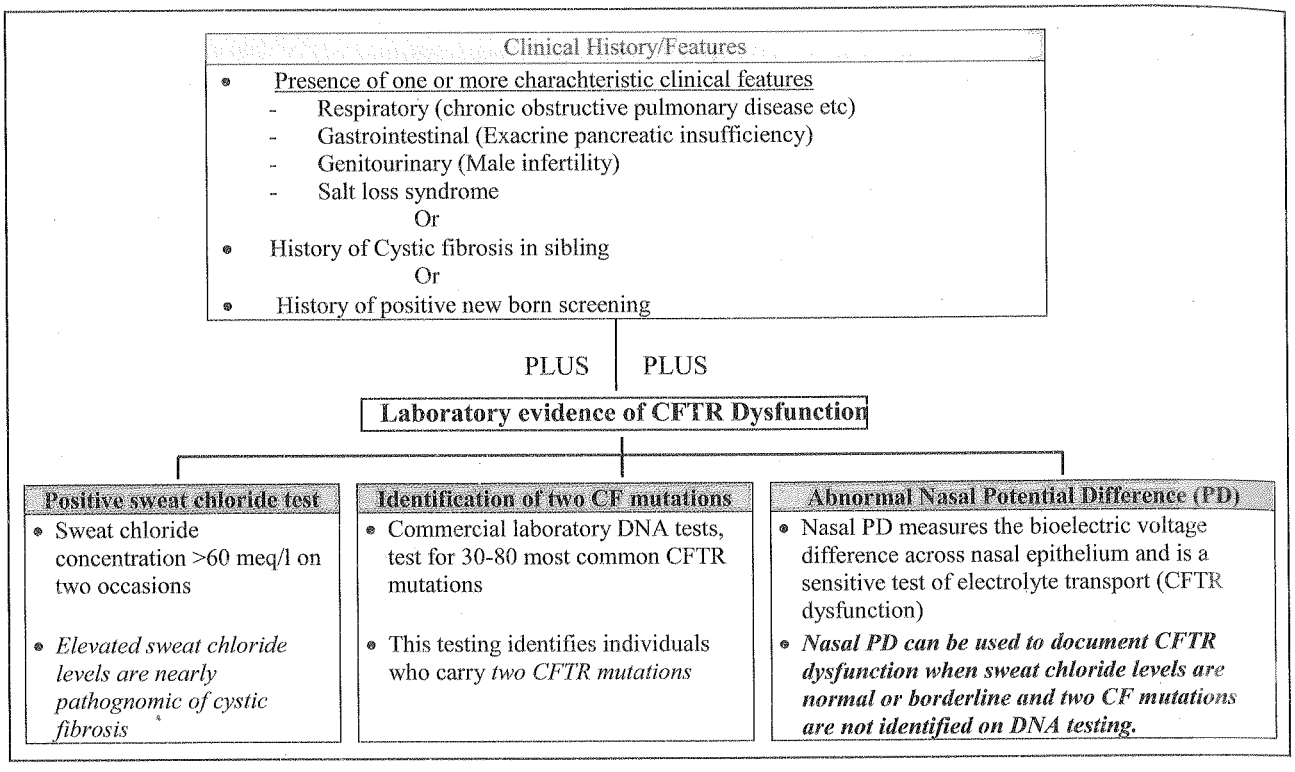
| Risk Factor For CF | PLUS | Laboratory Evidence of CFTR Dysfunction |
|---|---|---|
| • *Presence of one or more typical clinical feature (≥ 1 phenotypic symptom)* | Plus | • *Positive sweat chloride test (>60 mcq/l on two occasions)* |
| *or* | | *or* |
| • *History of CF in sibling* | Plus | • *Identification of 2 CF mutations* |
| *or* | | *or* |
| • *Positive Neonatal screening test* | Plus | • *Abnormal Nasal Potential Difference* |

***The patient in question*** *has typical clinical features of cystic fibrosis; however the sweat chloride levels are border line (between 40-60meq/l) on two separate occasions. To establish the diagnosis of cystic fibrosis, another laboratory evidence demonstrating CFTR dysfunction is therefore required.*

*This can be achieved by demonstration of abnormal CF mutation by DNA analysis or by demonstrating an abnormal nasal potential difference.*

*The diagnostic criteria for cystic fibrosis requires demonstration of at least two CF mutations and hence* ***demonstration of an abnormal F508 mutation alone is not sufficient to establish the diagnosis of CF***

***An abnormal CFTR nasal potential difference is an established laboratory evidence of CFTR dysfunction and is accepted as a diagnostic criterion to establish the diagnosis of cystic fibrosis.***




## Miscellaneous

**239. Answer is D (Acute Appendicitis):** *Sleisenger and Fordtran's Gastrointestinal and Liver Disease 10th/169*

***Alvarado score is used for diagnosis of Acute Appendicitis.***

**Alvarado score.**

The Alvarado score was developed in 1988 to stratify patients in need of surgical intervention for acute appendicitis and decrease delays in treatment and negative appendectomy rates. The Alvarado score is calculated based on 6 history and clinical examination findings and 2 laboratory values ***with an emphasis on right lower quadrant tenderness and leukocytosis for a total of l0 points.*** The Alverado score is not widely used.

**Alvarado scoring System for Acute Appendicitis**

| | | Alvarado Score |
|---|---|---|
| Symptoms | Migratory Right Iliac fossa pain | 1 |
| | Nausea/Vomiting | 1 |
| | Anorexia | 1 |
| Signs | Right Iliac Fossa Tenderness | 2 |
| | Elevation of temperature | 1 |
| | Rebound tenderness right iliac fossa | 1 |
| Laboratory | Leucocytosis | 2 |
| | Neutrophilic shift to the left (> 75%) | 1 |
| **Total score** | | 0-10 |

*An Alverado score of less than 5 (0-4) may be used to exclude a diagnosis of Acute Appendicitis. Patients with an Alverado Score >5 should be evaluated by a surgeon or undergo further imaging to confirm Acute Appendicitis. A patient with an Alverado Score > 6 (7 or more) is likely to require surgery (Patients with an Alverado Score of 5 or 6 may be observed*

| Score | Suggestion | Treatment |
|---|---|---|
| 0-4 | Unlikely Appendicitis | Look for other causes<br>May be used to exclude a diagnosis of Acute Appendicitis especially in Men |
| 5-6 | *Equivocal*<br>May Suggest Appendicitis | Should undergo further imaging for Acute Appendicitis<br>May be observed |
| 7-8 | *Probable*<br>Acute appendicitis is the probable diagnosis | Should undergo further imaging for Acute Appendicitis<br>Likely to require surgery |
| 9-10 | Likely<br>Acute appendicitis is the most likely diagnosis | Should undergo further imaging for Acute Appendicitis<br>Likely to require surgery |

**240. Answer is B (Appendicular Lump)**

***Ochsner-Sherren regimen is the expectant management giving to a patient with an appendix mass.***

*OchsnerSherren regimen refers to the expectant management giving to a patient with an appendix mass. Appendix mass (complication of acute appendicitis) is an inflammatory mass composed of edematous omentum, small bowel loops, cecum and sometimes sigmoid colon, all walling off an inflamed appendix. An appendix mass is a common surgical clinical entity, encountered in 2-6% of patients presenting with acute appendicitis. It is one of the earliest complications of acute appendicitis that can be managed without immediate operative intervention. At the beginning of the 20th century, Ochsner (1901) proposed initial non-operative management for such an appendix mass, followed by interval appendectomy 6-8 weeks after successful conservative management as proposed by Murphy at the beginning of the 20th century. This approach became a traditional management of appendicular mass and was popularly known as the 'OchsnerSherren regimen'. The aim of the OchsnerSherren regimen is to treat infection, relieve pain and supplement fluids and electrolyte over a period of 48-72 hours during which the clinician will expect the condition to improve. In 80-90% of the patients, the mass resolves without any complications. An interval appendectomy can then be performed 6-8 weeks after successful conservative management. The remaining 10-20% need emergency operation due to spreading infection*

**241. Answer is B (B. cereus) :** *Harrison 18th/p 312 CMDT 2008 / 482*

***Bacillus cereus causes non invasive diarrhea due to preformed enterotoxins.***
*Shigella, Salmonella and Y. enterocolitica are causes of invasive diarrhea.*

Bacterial Diarrhea

**Non Invasive**

- Non invasive diarrhea is caused by the release of toxins from bacteria that disrupt the secretory process
- This diarrhea is charachterized by the presence of watery stools

Blood and fecal leucocytes are charachteristically bsent

**Bacteria associated with Non Invasive Diarrhea**

- *Staphylococcus Aureus (Preformed toxin)*
- *Bacillus cereus (Preformed toxin)*
- *Clostridium perfringes (preformed toxin)*
- *ETEC (Enterotoxigenic E.coli)*
- *Vibrio cholerae*

**Invasive**

- Invasive diarrhea is caused by damage to gastrointestinal tissue (colonic tissue) due to direct invasion by bacteria
- This diarrhea is charachterized clinically by the presence of
  - Fever
  - Bloody stools (Dysentry)
  - Fecal leucocytes.

**Bacteria associated with Invasive diarrhea**

- ***Shigella***
- ***Salmonella***
- ***Yersenia Enterocolitica***
- *Entero invasive E.coli (ETEC)*
- *Aeromonas*
- *Plesiomonas*
- *Listeria monocytogenes*

**242. Answer is C (Reduces with fasting):** *CMDT 2009/499; Manual of Gastroenterology 4th/184 – Harrison 18th/p 321 Harrisons 17th/249*

*Secretory diarrhea does not reduce with fasting.*

*In secretory diarrhea an abnormal ion transport occurs across intestinal epethelial cells. This diarrhea is not related to the intestinal content and hence it typically does not cease with fasting.*

| Typical Features of Secretory Diarrhea |
|---|
| • ***Large volume (typically > 1L/ day)*** |
| • ***Little change with fasting*** *(Diarrhea typically does not cease while patient fasts)* |
| • ***Normal stool osmotic gap*** *(osmolality of stool is close to osmolality of plasma)* |
| • *No anion gap* |
| • *Stools are watery in consistency and do not contain pus or blood* |
| • ***Painless*** |



**243. Answer is A (Cisapride):** *Harrison 18th/46; Drug Induced Long QT syndrome (2002)/45; 'The Chemotherapy Source Book (Lippincott) 4th/605*

***Co-administration of ketoconazole with cisapride is contraindicated secondary to an increased risk of cardiovascular adverse effects such as 'torsades-de-pointes', ventricular tachycardia or ventricular fibrillation'.***
*(Taken from 'The Chemotherapy Source Book (Lippincott) 4th/605)*

**Ketoconazole and Prolonged QT interval**

- Ketoconazole has been reported to be pro-dysrhythmic (prolonged QT interval) even without the concomitant use of other drugs that cause prolongation of the QT interval.

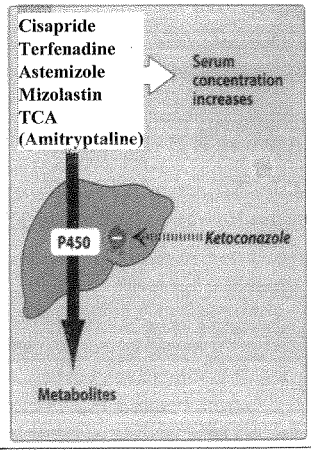
  *Ketoconazole alone can prolong the QT interval and induce Torsades-de-pointes by blocking the rapid component of delayed rectifier potassium channels (IKr)4.*

- Ketoconazole also *inhibits the cytochrome P450 CYP3A4 isoenzyme.*

- Ketoconazole ***should not be co-administered with another QT prolonging drug that is metabolized by the cytochrome P450 CYP3A4 isoenzyme such as Cisapride****, Terfenadine, Astemizole, or Amitryptyline as this will result in increased concentration of the latter leading to marked prolongation of QT interval and increase the risk of Torsades-de-pointes and life threatening ventricular arrythmias.*

**Important QT prolonging drugs metabolized by CYP3A4**
*Contraindicated for co-administration with Ketoconazole, Itraconazole, Erythromycin, Clarithromycin*

- *Cisapride*
- *Terfenadine*
- *Astemizole*
- *Mizolastin*
- *TCA (Amitryptaline)*




**Drugs with High Risk of Generating Pharmakokinetic Interactions** *(Harrison's 18th/ 46)*

| Drug | Mechanism | Examples |
|---|---|---|
| Antacids<br>Bile acid sequestrants | Reduced absorption | Antacids/tetracyclines<br>Cholestyramine/digoxin |
| Proton pump inhibitors<br>$H_2$ –receptor blockers | Altered gastric pH | Ketoconazole absorption decreased |
| Rifampin<br>Carbamazepine<br>Barbiturates<br>Phenytoin<br>St. John's wort<br>Glutethimide | Induction of Hepatic Metabolism | Decreased concentration and effects of :<br>Warfarin<br>Quinidine<br>Cyclosporine<br>Losartan<br>Oral contraceptives<br>Methadone |
| Tricyclic antidepressants<br>Fluoxetine<br>Quinidine | Inhibitors of CYP2D6 | Increased effect of many β blockers<br>Decreased codeine effect |

| | | |
|---|---|---|
| Cimetidine | Inhibitor of multiple CYPs | Increased concentration and effects of<br>Warfarin<br>Theophylline<br>Phenytoin |
| ***Ketoconazole***, Itraconazole<br>Erythromycin, Clarithromycin<br>Calcium channel blockers<br>Ritonavir | Inhibitor of CYP3A | Increased concentration and toxicity of some HMG-CoA reductase inhibitors, *cyclosporine*, ***cisapride***, *terfenadine (now withdrawn)*<br>Increased concentration and effects of indinavir (With ritonavir)<br>Decreased clearance and dose requirement for cyclosporine (with calcium channel blockers) |
| Allopurinol | Xanthine oxidase inhibitor | Azathioprine and 6-mercaptopurine toxicity |
| Amiodarone | Inhibitor of many CYPs and of P-glycoprotein | Decreased clearance (risk of toxicity) for<br>Warfarin<br>Digoxin<br>Quinidine |
| Gemfibrazole (and other fibrates) | CYP3A inhibition | Rhabdomyolysis when co-prescribed with some HMG-CoA reductase Inhibitors |
| Quinidine<br>Amiodarone<br>Verapamil<br>Cyclosporine<br>Itraconazole<br>Erythromycin | P-glycoprotein inhibition | Risk of digoxin toxicity |
| Phenylbutazone<br>Probenecid<br>Salicylates | Inhibition of renal tubular transport | Increased risk of methotrexate toxicity with salicylate |

**244. Answer is E (Hemorrhoids):** *Harrison 17th/259*

***'Hemorrhoids are probably the most common cause of Lower GIBleed (LGIB)'*** *– Harrisons*

**245. Answer is A (Colonoscopy):** *'Primary Care Medicine' by Goroll & Mulley (Lippincott) 6th/522; 'General Surgical Operations' by Kirk (Elsevier) 2006/228*

***Colonoscopy is the investigation of choice in elderly patients presenting with occult fecal blood and anemia to evaluate the possibility of a colorectal cancer.***

*'Colonoscopy is the test of choice in a case with occult fecal blood, rectal bleeding, anemia, or weight loss in an older patient, all of which suggest the possibility of colorectal cancer' - 'Primary Care Medicine' (Lippincott)6th/522*

*'In elderly patients who often tolerate barium enema badly, colonoscopy should be the first-line investigation for unexplained rectal bleeding or anemia* ***and is the investigation of choice for all patients with a positive fecal occult blood test'*** *- General surgical operations by Kirk (Elsevier) 2006/228.*

**246. Answer is A (Diverticulosis) :** *Harrison 14th/247; Harrison 15th/253; (Not elaborated in Harrison 16th)*

***Although anorectal disease is the most commonm cause of bleeding per rectum in the elderly, these lesions usually cause small amount of 'bright red' blood on the surface of stool and toilet tissue (small bleeds).***
***Diverticulosis may give rise to massive colonic bleed. The usual presentation of diverticular hemorrhage is that of brisk painless passage of a maroon coloured stool. It is the most common cause of massive bleeding per rectum in those above 55 years of age and hence the answer here.***

| **Common causes of Acute Lower G.I. bleeding (in descending order) over 55 years of age are :** |
|---|
| 1. Anorectal disease : Haemorrhoids and fissures |
| 2. Diverticulosis |
| 3. Angiodysplasia |
| 4. Polyps and Cancer |
| 5. Enterocolitis |

**247. Answer is B (Acute mesentric ischaemia) :** *Harrison 14th/1652, 15th/1699, 16th/1798; Bailey Love 23rd/1074*

***The onset of abdominal pain and maroon stools in an elderly patient with the background of ischaemic heart disease and atherosclerosis suggests the diagnosis of acute mesenteric ischemia.***

***'The most important clue to an early diagnosis of acute mesentric ischaemia is the sudden onset of severe abdominal pain in a patient with atrial fibrillation or atherosclerosis'*** *- Harrison*

The patient in question : is an ***old man of 60 yrs***, who has a ***history of I.H.D. & atherosclerosis*** & ***presents with abdominal pain*** thus leading us towards this diagnosis

Major clinical features of acute mesentric ishcaemia are :

1. ***Severe abdominal pain***, often colicky & periumbilical at onset, later becoming diffuse
2. Vomiting, anorexia
3. Diarrhoea and / or constipation

Examination of the abdomen reveals: Tenderness & distension.

*Two features are important to be observed*

- ***Bowel sounds are often normal even in face of severe infarction.*** Q
- ***Gross haemorrhage is unusual*** Q (except in ischaemic colitis) Q

Gastrointestinal bleeding therefore is mild and accounts for the maroon stools in our patient.

**248. Answer is D (All of the above):** *Harrison 15th / 1697*

***Intestinal hypomotility may be seen in all conditions mentioned in the questions.***

| | |
|---|---|
| Parkinsonism | • Achalasia / Pseudo-obstruction / Megacolon<br>• Lewy bodies in myenteric plexus of esophagus and colon |
| Diabetes Mellitus | • Gastroparesis and intestinal & colonic dysmotility<br>• Myenteric plexus morphologically intact |
| Amyloidosis | • Achalasia / Gastroparesis / Pseudo-obstruction<br>• Amyloid deposit in both smooth muscle and myenteric plexus |

**249. Answer is D (Hyperthyroidism):** *Surgical Pathology of the GI Tract, Liver, Biliary Tract, and Pancreas (Elsevier Health Sciences, 2009)/ 103*

***Hyperthyroidism is associated with increased gastric and intestinal motility while Hypothyroidism is associated with decreased gastric and intestinal motility.***

| | |
|---|---|
| Hyperthyroidism | Hypermotility: diarrhea or steatorrhea |
| Hypothyroidism | Decreased motility: reflux, bezoars, ileus, constipation |

**250. Answer is D (Hyperthyroidism):** *Surgical Pathology of the GI Tract, Liver, Biliary Tract, and Pancreas (Elsevier Health Sciences, 2009)/ 103*

***Hyperthyroidism is associated with increased gastric and intestinal motility while Hypothyroidism is associated with decreased gastric and intestinal motility.***

**251. Answer is C (Hyponatremia):** *A practical Guide to Pediatric Emergency Medicine (Cambridg Univ. Press) 2011/chap. 54; Pediatric Medical student USMLE Board part II & III & IV (John Barlett 1999/46, 47.*

***The most common cause of seizures in children with diarrhea is hypovolemic hyponatremia.***

*Diarrhea may be associated with hypovolemic hyponatremia or hypernatremia from hypotonic fluid loss. Both hyponatremia and hypernatremia may manifest with seizures. However Hyponatremia remains the most common electrolyte abnormality in diarrhea encountered in clinical practice and is hence the single best **Answer** of choice amongst the options provided.*

**252. Answer is D (50% involve rectum) :** *Surgical Pathology by Noel Weidner /230*

***'2/3 of lesions are located in the caecum and ascending colon and one quarter in the left colon'.***

*Thus involvement of left side of colon (or rectum) is uncommon and certainly less than 50% of cases involve rectum.*

**Telengiectasias consist of dilated capillaries that appear clinically as erythematous to violaceous vessels.**

**Telengiectaseas in colon may most commonly be due to:**

1. Vascular ectasia / Angiodysplasia
   - **Angiodysplasia is a telengiectasia** of thin walled capillaries and venules in the mucosa and submucosa of colon
   - **Mean age at diagnosis is approx. 65 years** but cases **have occured in the young.**
   - **2/3 of lesions are located in coecum and ascending colon** and **one quarter in the left colon.**
2. Radiation : Telengiectaseas are the most common long term effect of radiation.
3. Hereditary hemorrhagic telengiectaseas - affect **younger patients** with a positive family history.

**253. Answer is C (Pernicious anemia) :** *Harrison's 16th/604*

*Pernicious anemia is associated with Hypergastrinemia and Hypochlorhydria.*

**Pernicious anemia**

- It is the most common cause of vitamin B12 deficiency in temperate climate[Q]
- It is characterised by gastric atrophy [Q] affecting the acid and pepsin secreting portion of stomach i.e. fundus and body. Antrum is spared.
  - intrinsic factor required for absorbtion of vit B12 is secreted by perietal cells, present in body and fundus of stomach and therefore ***intrinsic factor is depleted***.
  - acid secreting cells are situated in body and fundus of stomach and therefore **acid is depleted - Achlorhydria**
  - gastrin producing G cells are situated in the antrum of stomach and so spared and therefore **depletion of gastric acid results in hypertrophy of G-cells and hypergastrinemia - Hypergastrinemia**

**254. Answer is C (Pernicious anemia) :** *Harrison's 15th/677; Harrison 14th/655, 656; Harrison 16th/604*

*Depletion of gastric acid (Hypochlorhydria) results in hypertrophy of G-cells and hypergastrinemia*

**Perenicious anemia**

- It is the most common cause of vitamin $B_{12}$ deficiency in temprate climate[Q]
- It is characterised by gastric atrophy[Q] affecting the acid and pepsin secreating portion of stomach i.e. fundus and body. Antrum is spared.
  - intrinsic factor required for absorbtion of vit B12 is secreted by perietal cells, present in body and fundus of stomach and therefore ***intrinsic factor is depleted***.
  - acid secreting cells are situated in body and fundus of stomach and therefore **acid is depleted achlorhydria**
  - gastrin producing G cells are situated in the antrum of stomach and so spared and therefore **depletion of gastric acid results in hypertrophy of G-cells and hypergastrinemia**

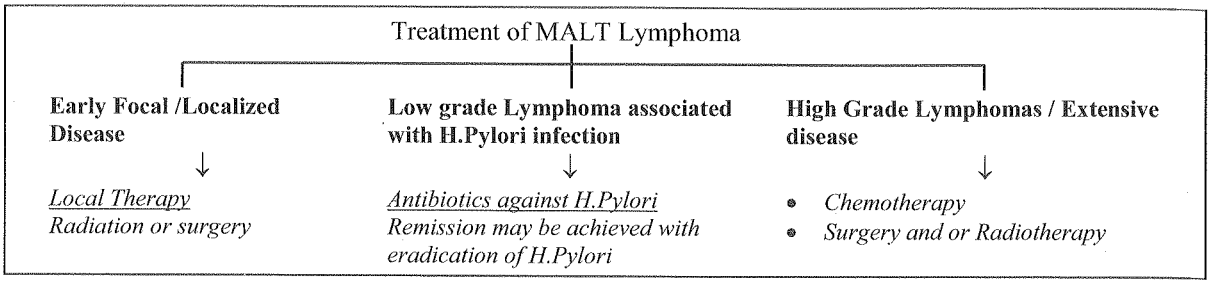
**255. Answer is B (Esophagus varices)** *Harrison 16th /e p. 1863, 235 ; Harrison 17th 1976-1977 Harrison 18th/p 2597, 2598*

*'Massive haematemesis in the background of splenomegaly suggests variceal bleed due to portal hypertension.'*

**256. Answer is C (Present as stromal polyps):** *Harrison 18th/p 928 Harrisons 17th / 694; Current Diagnosis & Treatment in Gastroenterology 2nd/389; Oxford Text book of Medicine 4th/589*

***Stromal polyps are infrequent primary gastric malignancies classified as Gastrointestinal Stromal Cell Tumors (GSIT). These are not associated with MALT Lymphomas***

- **MALT Lymphomas presents at extranodal sites** (Harrisons)
  *MALT Lymphomas are also called 'Extranodal Margmal zone B cell Lymphomas of MALT type' and typically occur at extranodal sites as suggested by the terminology*
- **MALT Lymphomas are predisposed by H.Pylori** (Harrison)
  *Gastric presentation of MALT Lymphoma is associated with H. Pylori infection – Harrisons*
- **MALT Lymphomas are sensitive to chemotherapy**
  *Extensive MALT Lymphomas are most often treated with single agent chemotherapy such as chlorambucil- Harrison*




**257. Answer is B (Amylase levels):** *Washington Manual of surgery 5th / 413, Bailey 25th / 1425*

***The major advantage of Bladder drainage is the ability to measure urinary amylase which can facilitate early diagnosis of rejection.***

*'Urinary drainage of the pancreas has the advantage that urinary amylase levels can be used to monitor graft rejection'*
*- Bailey 25th / 1425*

**Exocrine Drainage after Pancreatic Transplantation**

| Enteric Drainage | Bladder Drainage |
|---|---|
| The whole pancreas along with a segment of donor duodenum is transplanted into the recipient small bowel<br>All exocrine secretions / enzymes are drained into the bowel and excreted with the stool<br>**Major Advantage of Enteric Drainage (Disadvantage of Bladder Drainage)**<br>• Fewer Urinary tract infections /Urological complications (Urological complications are more common with bladder drainage)<br>• Fewer Metabolic complications (eg Acidosis) (Metabolic complications such as metabolic acidosis are more common with bladder drainage)<br>• Lesser incidence of Reflux Pancreatitis (Reflux Pancreatitis is more common with bladder drainage) | The whole pancreas along with a segment of donor duodenum is transplanted into the recipient bladder<br>All exocrine secretions / enzymes are drained into the bladder and excreted via urine<br>**Major Advantages of Bladder Drainage (Disadvantage of Enteric drainage)**<br>• *Ability to measure urinary amylase which can facilitate early diagnosis of rejection*<br>(A fall in urinary amylase usually precedes a rise in systemic blood glucose during rejection such that anti-rejection treatment can be commenced sooner)<br>• Lower rate of Technical failure (Procedure related complications) |

**258. Answer is A (End colostomy) :** *PreTest Surgery 11th/299; Schwartz 8th/1074; 'Intestinal Failure' by Nightingale (2001)/62*

***Parastomal hernia is the most frequent complication of End Colostomies.***

*Parastomal hernia is common around an end colostomy particularly if the stoma brought out is lateral to the rectus sheath and if the abdominal musculature is very weak as often occurs in the elderly.*

**Facts to Remember**

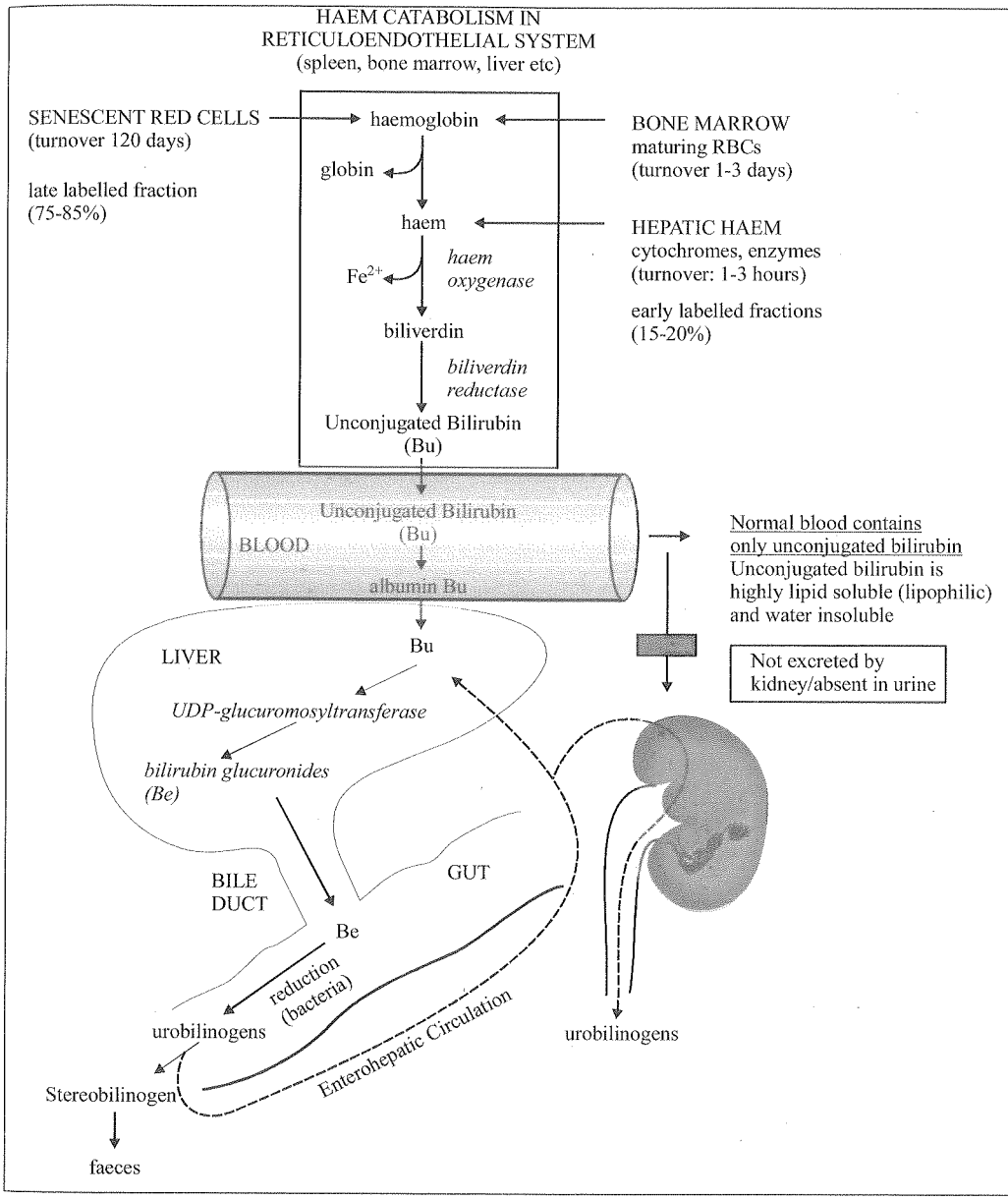
- *Parastomal hernias are more common after a colostomy than after on Iliostomy*
- *Parastomal hernias are most frequently seen in association with end colostomies that are brought out lateral to the rectus muscle*
- *'Prolapse' are more common after a colostomy than after an Iliostomy*
- *'Prolapse' is most commonly seen after 'loop colostomies' particularly loop transverse colostomies.*

# Liver and Biliary Tract

## ESSENTIAL REVISION NOTES

# Jaundice

## Catabolism of 'Haem' and Generation of Bilirubin




- **Haemoglobin**in the reticuloendothelial system is broken down into haem and converted into unconjugated bilirubin
- **Unconjugated bilirubin** present in blood is complexed with albumin to make it soluble in blood and transport it to the liver. However, the glomerulus does not allow the albumin bilirubin complex to filter and *hence bilirubin does not appear in urine.*
- **Conjugated bilirubin** is formed in the liver and directly excreted into the GIT through bile where it is reduced to urobilinogen and stercobilinogen. Conjugated bilirubin does not normally circulate in the blood at all and hence despite being filterable and water soluble it does not appear in urine.

# Pathophysiology of different types of jaundice

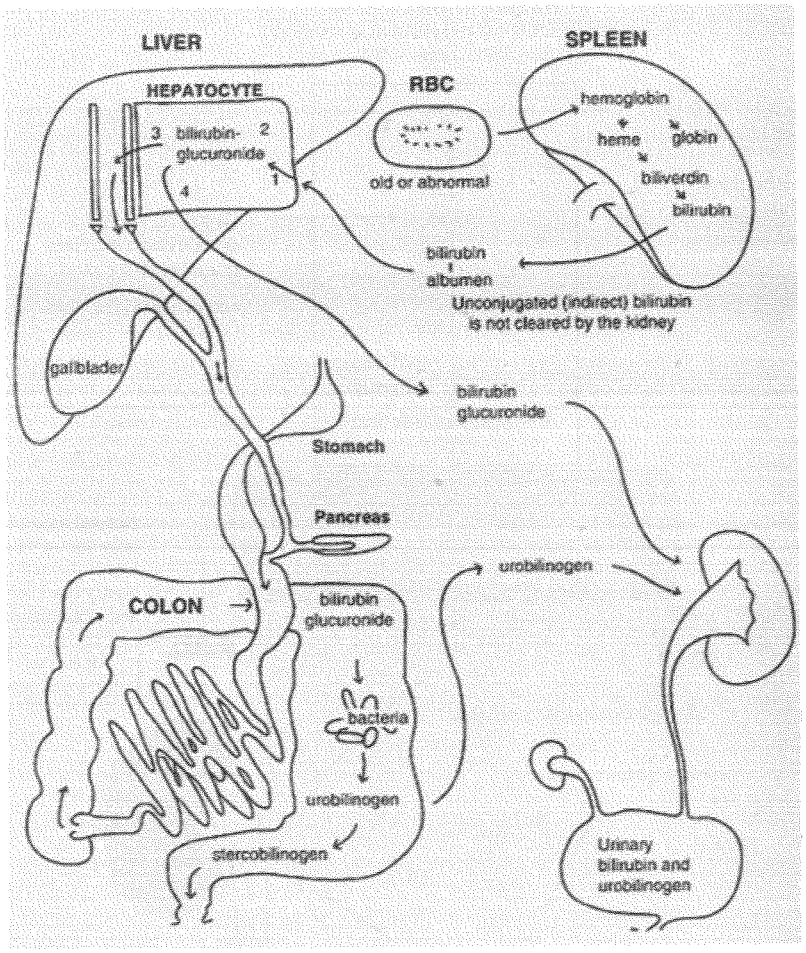
## Pathophysiology of different types of jaundice

- Normal blood contains unconjugated bilirubin only (no conjugated bilirubin)

> *Unconjugated bilirubin is water insoluble (lipophilic, lipid soluble) and not filterable by the kidney.*

- Unconjugated bilirubin is taken up from the systemic circulation by hepatocytes (1)
- Unconjugated bilirubin is then conjugated to bilirubin glucoronide by glucoronyl transferase within the hepatocytes (2)
- Conjugated bilirubin is then excreted into the bile from where it reaches the GIT (3)
  *This is the rate-limiting step.*

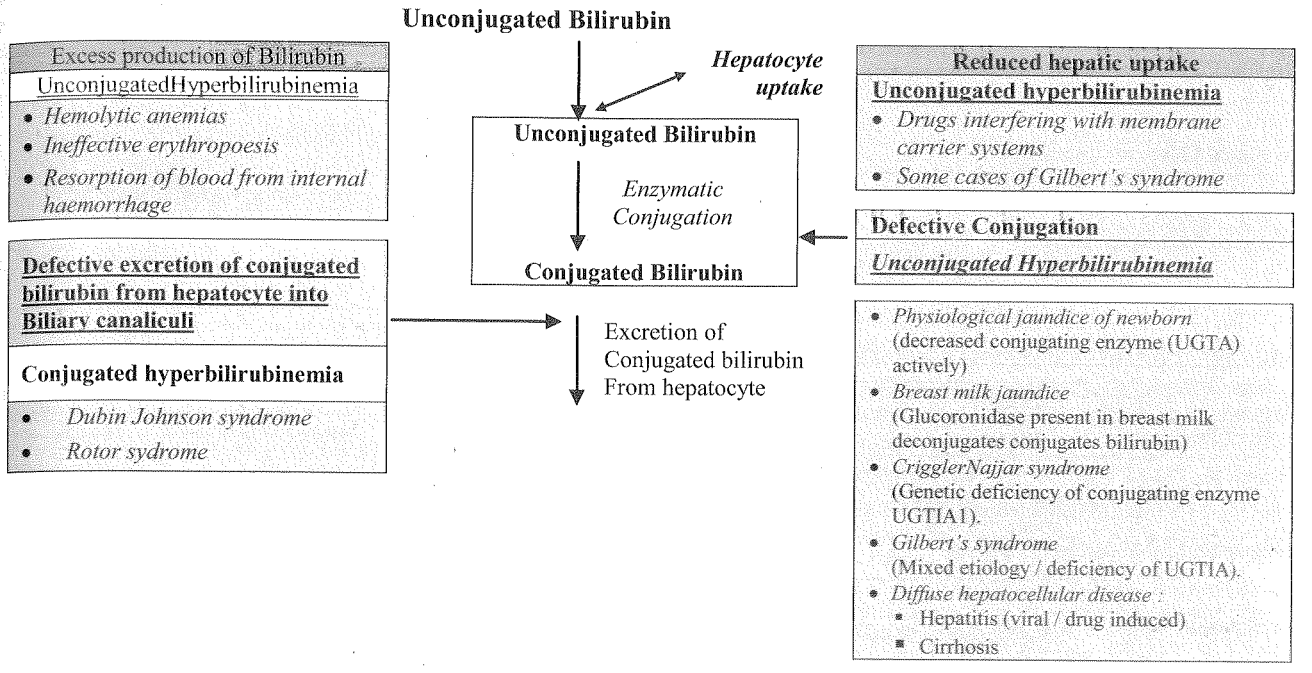
> *Conjugated bilirubin is water soluble and filterable by the kidney*
> **Normally,** there is no conjugated bilirubin in the systemic circulation and hence no bilirubin is filtered in the kidney or present in the urine.
> ***Abnormally***
> When there is hepatocellular dysfunction or bile flow is totally obstructed, conjugated bilirubin "leaks" into the systemic circulation
> This conjugated bilirubin may now be excreted by the kidney and be detected in urine.
> **Bilirubin in urine (bilirubinuria)**
> *Presence of bilirubin in urine suggests a diagnosis of conjugated hyperbilirubinemia either due to hepatocellular jaundice or obstructive jaundice.*




- Within the GIT conjugated bilirubin is degraded/reduced to urobilinogen and then to stercobilinogen

> Urobilinogen is water soluble and filterable by the kidney
> **Normally,** a small portion of the urobilinogen is reabsorbed from the gut and excreted by the kidney (<4 mg/day)
> **In Non-Obstructive Hyperbilirubinemia (hemolytic, hepatocellular)** the amount of urobilinogenexreated by the kidney is increased as more urobilinogen is formed and reabsorbed.
> ***Elevated levels of urobilinogen suggest primarily an non obstructive hyperbilirubinemia***
> **In Obstructive Hyperbilirubinemia**, conjugated bilirubin does not reach the GIT and hence no urobilinogen is formed
> ***Absent levels of urobilinogen suggest a diangnosis of obstructive hyperbilirubinemia***

## Causes and Classification of Hyperbilirubinemia




| Indirect hyperbilirubinemia |
|---|
| Hemolytic disorders |
| Inherited<br>• *Spherocyteosis,*<br>• *Elliptocytosis*<br>• *Glucose-6-phosphate dehydrogenase*<br>• *Pyruvate kinase deficiencies*<br>• *Sickle cell anemia*<br>Acquired<br>• *Microangiopathic hemolytic anemias*<br>• *Paraoxysmal nocturnal hemoglobinuria*<br>• *Immune* hemolysis |
| Ineffective erythropoiesis |
| • *Cobalamin and folate deficiency*<br>• *Severe iron deficiency*<br>• *Thalassemia* |
| Drugs |
| • *Rifampicin,*<br>• *Probenecid,*<br>• *Ribavirin* |
| Inherited conditions |
| • *Crigler-Najjar types I and II*<br>• *Glibert's* syndrome |

| Direct hyperbilirubinemia |
|---|
| Inherited conditions |
| • *Dubin-Johnson syndrome*<br>• *Rotor's* syndrome |

## Biochemical markers in various types of Jaundice

| Condition | Serum Bilirubin | Urine Urobilinogen | Urine Bilirubin | Fecal urobilinogen |
|---|---|---|---|---|
| Normal | Direct 0.1-0.4 mg/dl<br>Indirect 0.2-0.7 mg/dl | 0-4 mg/24 h | Absent | 40-280 mg/24h |
| Hemolytic anemia<br>(Unconjugated Hyperbilirubinemia) | ↑ Indirect | Increased | Absent | Increased |
| Obstructive jaundice<br>(Conjugated hyperbilirubinemia) | ↑ Direct | Absent | Present | Trace to absent |
| Hepatitis | ↑ Direct and indirect | Decreased if micro-obstruction is present | Present if microobstruction occurs | Decreased |

**Distinguishing features between various forms of Jaundice:**

| Parameter | Hemolytic | Hepatocellular | Obstructive |
|---|---|---|---|
| **Blood** | **Blood** | **Blood** | **Blood** |
| Haemoglobin (12-18 g/dl) | Decreased | N. | N. |
| Unconjugated bilirubin (0.2 to 0.7 mg/dl) | ↑↑ | N or ↑ | N |
| Conjugated bilirubin (0.1 to 0.3 mg/dl) | N | ↑ | ↑ |
| Alkaline phosphatase (3-13 KAU) (30 to 120 IU/L) | N | N or ↑ | ↑↑ |
| Aminotransferases | N | ↑↑ | N |
| Cholesterol | N | N | ↑ |
| **Stool** | **Stool** | **Stool** | **Stool** |
| Colour of stool | N | N | Pale |
| **Urine** | **Urine** | **Urine** | **Urine** |
| Bilirubin | 0 | ↑ | ↑ |
| Urobilinogen | ↑ | ↑ | ↓ |

## Approach to a patient presenting with bilirubinemia

Hyperbilirubinemia

| Unconjugated Hyperbilirubinemia | Conjugated Hyperbilinubinemia |
|---|---|
| Direct bilirubin < 15%<br>Indirect bilirubin > 85% | Direct bilirubin > 15%<br>Indirect bilirubin < 85% |

Approach to a case of Hyperbilirubinemia (Jaundice)

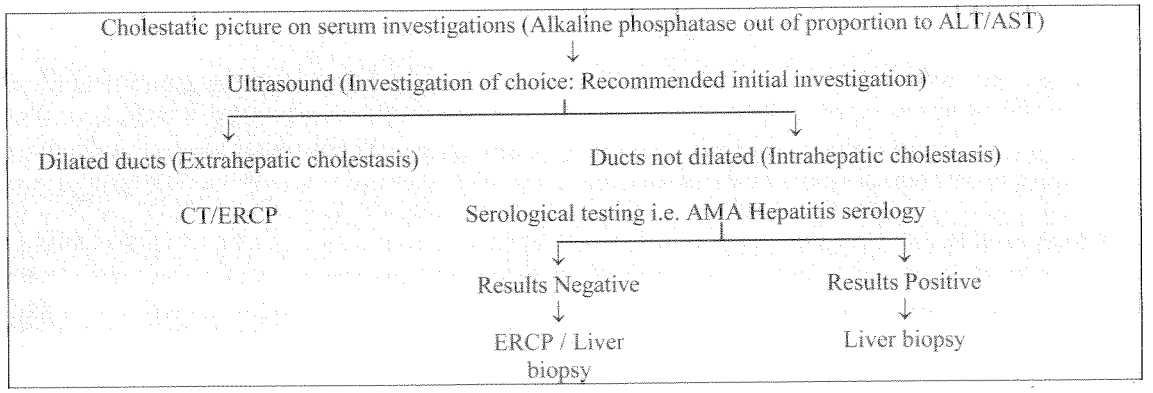
- Isolated elevation of bilirubin
  - Direct/conjugated hyperbilirubinemia (Direct > 15%)
    - Inherited disorders:
      1. Dublin Johnsons
      2. Rotors
  - Indirect/unconjugated hyperbilirubinemia (Direct < 15%)
    1. Haemolytic disorders
    2. Ineffective erythropoiesis
    3. **Drugs:** Rifampicin, Probenecid
    4. **Inherited disorders**
       Gilbert's syndrome
       CriglerNajgar syndrome
- Bilirubin elevated along with derangement in other liver tests. i.e. ALT/AST & Alkaline phosphatase
  - ALT/AST elevated out of proportion to Alkaline phosphatase
    - Hepatocellular Cause
      1. Viral hepatitis
      2. Toxic hepatitis
      3. Wilson's disease
      4. Cirrhosis
  - Alkaline phosphatase elevated out of proportion of AST/ALT
    - Obstructive cause
      - Extrahepatic cholestasis
      - Intrahepatic cholestasis

## Further Approach to a patient with direct hyperbilirubinemia

*If direct conjugated bilirubin is greater than 15% of the total bilirubin, it is termed as direct bilirubinemia*

| Bilirubin | Associated parameter | Inference |
|---|---|---|
| Direct bilirubinemia | Alkaline phosphatase raised out of proportion to transferases (ALT/AST) | Cholestatic obstructive jaundice |
| Direct bilirubinemia | Transferases (ALT/AST) Raised out of proportion to alkaline phosphatase | Hepatocellular jaundice |

## Further Protocol for investigating a patient with cholestatic serum profile.




***Initial investigation of choice in a case of obstructive jaundice is: ULTRASONOGRAPHY***

## Hepatic Enzymes and their role in determining cause of Hyperbilirubinemia

**Liver Enzymes**

| Enzymes that Reflect damage to Hepatocytes | Enzymes that Reflect Cholestasis |
|---|---|
| *ALT (SGPT)*<br>*AST (SGOT)*<br>*LDH* | • *Alkaline Phosphatase (AIP)*<br>• *5' Nucelotide (5' N)*<br>• *Gamma GlutamylTransferase* |
| ***ALT** is found primarily only in the liver and is hence more specific than AST.*<br>***AST** is found in several other tissues besides liver including heart muscle, kidney brain, pancreas, lungs leucocytes and erythrocytes.* | *ALP and 5'N are more specific than GGT.* |

*Note that true assessment of hepatic excretory function requires measurement of serum concentration of substances metabolized and transported by the liver or by determination of rate of clearance of exogenously administered dyes or drugs such as indocyanine green, caffeine, lidocaine and PABA.*

*Liver enzymes including those reflecting cholestasis are not true measures for detecting excretory function of hepatocytes.*

## Hereditary Hyperbilirubinemias

***Hereditary Hyperbilirubinemias*** $^{Q}$

| **Unconjugated** | **Conjugated** |
|---|---|
| (Defect conjugating enzyme bilirubin glucoronyltransferase) | (Defect in biliary excretion of conjugated bilirubin) |
| 1. CirglerNajjar Syndrome type I & type II $^{Q}$ | 1. Dubin Johnson syndrome $^{Q}$ |
| 2. Gilberts syndrome $^{Q}$ | 2. Rotor's syndrome $^{Q}$ |

*Rotor's syndrome is an Autosomal recessive inherited disorder characterized by a defect in biliary excretion leading to Conjugated Hyperbilirubinemia.*

*Dubin Johnson Syndrome results from a hereditary defect in excretion of conjugated bilirubin across the canalicular membrane and leads to conjugated hyperbilirubinemia.*

***Rotor's syndrome and Dubin Johnson syndrome** are characterized by defective excretion of conjugated Bilirubin. They thus present with a picture similar to obstructive with the following exceptions:*
- *Alkaline phosphatase is not raised.*

*Gilberts syndrome and CriglerNajjarsyndromepresent with unconjugated hyperbilirubinemia due to defect in the conjugating enzyme bilirubin glucoronyltransferase*

Urinary Urobilinogens are however not elevated in these conditions. *Urobilinogen may never the less be present in urine (N or ↓) in these conditions*

*Gilberts syndrome and CriglerNajjar syndrome are enymatic disorders charachterized by defective conjugation. These disorders may present with a picture similar to hemolytic jaundice with unconjugated hyerbilirubinamia, with the following exceptions.*
- *Haemoglobin is not decreased*
- *Urobilinogen is not increased (Normal or Decreased)*

**Unconjugated Hyperbilirubinemia with elevated urobilinogen levels of urine is characteristic of Hemolytic anemia**

| Condition / syndrome | Hyperbilirubinemia | Urinary Urobilinogen*(N=0-4 mg/24 hrs)* |
|---|---|---|
| *Hemolytic Anemia* | *Unconjugated (Indirect)* | *Increased* |
| *Gilbert's syndrome* | *Unconjugated (Indirect)* | *Normal or Decreased* |
| *CriglerNajjar* | *Unconjugted (Indirect)* | *Normal or Decreased* |

## Dubin Johnson Syndrome : Review

During Johnson syndrome is an ***autosomal recessive***[Q] hereditary disorder presenting with ***conjugated hyperbilirubinemia***[Q] due to ***defect in hepatic excretory function across the canalicular membrane of hepatocyte.***[Q]

**Clinical presentation**

- Most patient are asymptomatic (subclinical chemical hyperbilirubinemia)
- ***Unexplained low grade jaundice during teenage years Often exacerbated by :***
  - ***Oral contraceptive use***
  - Pregnancy
  - Intercurrent illness
- Physical examination is usually normal (occasional patient may have hepatosplenomegaly)

**Laboratory studies**

- ***Conjugated Hyperbilirubinemia*** : Total bilirubin is ***typically between 2 – 5 mg/dl*** *(34 – 85 µmol/L)*

*May occasionally be Normal or as high as 20-25 mg/dl(340-430 µmol/L)*

- **Bilirubinuria** : Typically present as hyperbilirubinemia is conjugated
- ***Other Routine Liver Function Tests including Serum Transaminases and Alkaline Phosphatase are essentially Normal***

**Diagnosis**

**Bromsulphaleintest**:*Elaborated above*

**Corporphyrin test**
**(Preferential urinary excretion of corporphyrin-I)**

Corporphrins are byproducts of hemebiosnthesis
There are two naturally occurring corporphyrins – I & III
***Normally approx. 75 % of corporpyrin in urine is isomer III***
***In urine of patients with D-J Syndrome total corporphyrin content in urine is norma but > 80 % is Isomer I***

**Histology :**

Deposition of melanin like pigment occurs in the liver causing ***liver to appear dark or completely black.***

*Pigment is thought to be derived from epinephrine metabolites that are not excreted normally*

## CriggerNajjar syndrome

*CriggerNajjar syndrome is primarily an autosomal recessive hereditary disorder charchterized by unconjugated hyperbilirubinemiadue to defect in the conjugating enzyme bilirubin glucoronyltransferase*

### Principal Characteristics Criggler-Najjar Syndromes

| Feature | Crigler-Najjar Syndrome | |
|---|---|---|
| | Type1 | Type II |
| Total serum bilirubin, µmol/L (mg/dl) | 310-755 (usually > 345)<br>[18-45 (usually >20)] | 100-430 (usually <345)<br>[6-25(usually <20)] |
| Routine liver tests | Normal | Normal |
| Response to Phenobarbital | None | Decreases bilirubin by>25% |
| Kernicterus | Usual | Rare |
| Hepatic histology | Normal | Normal |
| Bile characteristics | | |
| Color | Pale or colorless | Pigmented |
| Bilirubin fractions monoconjugates | >90% unconjugated | Largest fraction (mean: 57%) |
| Bilirubin UDP-glucuronosyl-transferase | Typically absent; traces in some patients | Markedly reduced:0-10% of normal |
| Inheritance (all autosomal) | Recessive | Predominantly recessive |

**Kernincterus** *is characteristic features of type I CrigglerNajjar syndrome; Kernincterus is extremely rare in Type II CrigglerNajjar syndrome.*
**Phenobarbital** *is extremely effective and useful in type II CrigglerNajjar syndrome and reduces bilirubin levels by > 25%.*

# Viral Hepatitis

## Diagnosis of Acute viral Hepatitis:

Diagnosis of Acute viral Hepatitis

**Prodromal Symptoms**

***Anorexia, Nausea, Vomiting***
*Fatigue, malaise, arthralgic, myalgia, Fever*

↓

**Clinical Jaundice and associated Signs**

- Clinical Jaundice (Also dark urine, clay coloured stool)
- ***Tender Hepatomegaly*** (Right upper abdomen pain/discomfort)

↓

**Characteristic Laboratory Parameters**

| Bilirubin | AST/ALT | Alkaline Phosphate | Albumin + Prothrombin time |
|---|---|---|---|
| Elevated (Both fractions may be elevated) | Elevated Elevated usually >500 IU/L ALT>AST | Normal to < 3 times normal (N=30 to 120 IU/L) (N=3 to 13 KAU) | Usually normal |

Note:
*ALT is synonymous with SGPT*[Q]
*AST is synonymous with SGOT*[Q]

## Pathology of Acute Viral Hepatitis:

Hepatocyte injury in Acute Hepatitis

| Ballooning degeneration | Cytolysis | Apoptosis (Acidophilic degeneration) |
|---|---|---|
| *Ballooning of Hepatocytes* | *Necrosis of hepatocytes* | ***Councilmann Bodies*** |

***Councilman bodies are acidophilic /eosinophilic apoptotic bodies seen in Acute Viral hepatitis and represent irreversible hepatocyte damage.***

## Pathology of Chronic Viral Hepatitis:

Histopathological Classification of Chronic Hepatitis

| **Chronic Active Hepatitis (Periportal or Interface Hepatitis)** | **Chronic Persistant Hepatitis (Portal Hepatitis)** |
|---|---|
| Chronic Hepatitis with histopathological features suggesting a progressive course<br>**Biopsy Features**<br>• *Hepatic architecture is distorted*<br>• *Inflammation extends beyond the portal tract (Portal tract infiltration is common with early portal tract fibrosis)*<br>• *Lamina Limitans is breached and hepatic lobules are invaded*<br>• *Piecemeal necrosis & bridging necrosis is typically seen in Lobules* | Chronic Hepatitis with histopathological features suggesting a beingn and self limiting course<br>**Biopsy Features**<br>• *Hepatic architecture is maintained*<br>• *Inflammation is limited to portal tracts (Portal tract infiltration is typical but portal tract fibrosis is minimal)*<br>• *Minimal/No breach of Lamina Limitans*<br>• *Minimal /No Piecemeal necrosis or Bridging necrosis in Lobules* |

**Clinical and epidemiologic features of viral hepatitis:**

| Features | HAV | HBV | HCV | HDV | HEV |
|---|---|---|---|---|---|
| **Incubation (days)** | 15-45 | 30-180 | 15-160 | 30-180 | 14-60 |
| **Age** | Children, young Adults | Young adults | Any age but more in adult | Any age | Young adults |
| **Transmission** | | | | | |
| *Fecal-oral* | +++ | --- | --- | --- | +++ |
| *Percutaneous* | Unusual | +++ | +++ | +++ | --- |
| *Perinatal* | --- | +++ | + | + | --- |
| *Sexual* | + | ++ | + | ++ | --- |
| **Clinical** | | | | | |
| *Severity* | Mild | Occasionally Severe | Moderate | Occasionally Severe | Mild |
| *Fulminant* | .1% | .1%-1% | .1% | 5-20% | 1-2% |
| *Progression to chronicity* | None | Occasional (1-10%) | Common (50-70%) | Common | None |
| *Carrier* | None ♀ | 01%-30% | 1.5 to 3.2% | Variable | None ♀ |
| *Cancer* | None ♀ | +nt | +nt | Variable | None ♀ |
| *Prognosis* | Excellent | Worse with age | Moderate | Acute: good Chronic: poor | Good |
| *Prophylaxis* | IgG Vaccine | HBIG Recombinant vaccine | None | - | Unknown |

♀ *HCV is the most common Virus associated with transfusion-associated hepatitis*
♀ *No vaccine / prophylaxis is available for HCV*
♀ *Malignant potential is present with HCV (also with HBV)*
♀*Progression to chronicity is seen with hepatitis B and Hepatitis C*
♀*Perinatal transmission is most significant with hepatitis B*
♀*Hepatitis B, C and D are essentially spread by parenteral routes.*
♀*HepatitisA& E are non-parenteral hepatitis.*
♀*Hepatitis B is not transmitted through fecal-oral route (stool).*
♀*Most common hepatitis to progress to chronicity is hepatitis C*
♀ *Most common cause of fulminant Hepatitis in pregnant women is Hepatitis E*
♀ *Most common cause of epidemic hepatitis is Hepatitis E*
♀ *Most common cause of sporadic hepatitis in adults is Hepatitis E*
♀ *Most common cause of sporadic Hepatitis in children is Hepatitis A*

**Anti-Liver Kidney Microsomal Antibodies (anti-LKM antibodies)**

*Anti-Liver Kidney Microsomal (LKM) antibodies* are detected in the sera of patients with different types of acute or chronic liver disease.
These antibodies are target against *Cytochrome P-450 components (antigens)*
*Three types of LKM antibodies* have been most extensively studied

| Microsomal Antibodies | Antigen | Disease |
|---|---|---|
| ***Anti-LKM1*** | Cytochrome P450 2D6 | • ***Autoimmune Hepatitis type II*** • ***Chronic Hepatitis C (10%)*** |
| ***Anti-LKM2*** | Cytochrome P450 2C9 | • ***Drug induced Hepatitis*** (Tienilic acid induced Hepatitis) |
| ***Anti-LKM3*** | Cytochrome P450 1A2 | • ***Chronic Hepatitis D*** |

# Hepatitis B

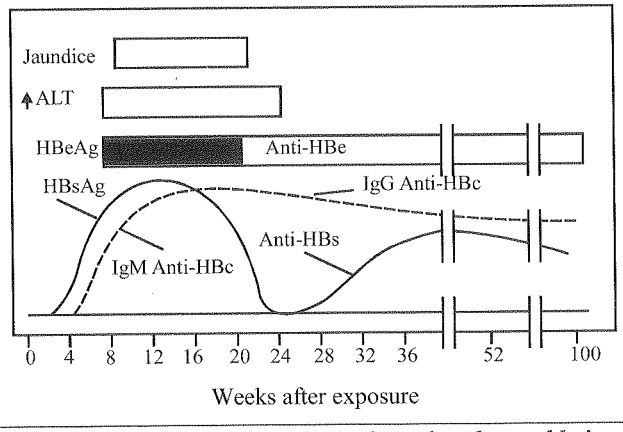
## Genomic structure of Hepatitis B:

| 'S' Gene | 'C' Gene | 'P' Gene | 'X' Gene |
|---|---|---|---|
| Codes for the envelope protein, Hbs Ag. | Codes for two nucleocapsid protein.<br>a. Hbc Ag: The intracellular core protein.<br>b. Hbe Ag: A soluble non particulatenucleocapsid protein. | Codes for DNA polymerase<br>This DNA polymerase has two acitivities:<br>a. DNA dependent DNA Polymerase<br>b. ***RNA dependent Reverse Transcriptase.*** | Codes for Hbx Ag.<br>It is a small non particulate protein, that can transactivate the transcription of cellular and viral gene. |

***The reverse transcriptase activity is a property of DNA polymerase which is coded by 'P' gene***

## Serology of Hepatitis B

| Hbs Ag | Anti Hbs Ag |
|---|---|
| Indicates that the person is infected with the virus. The infection may manifest as 'disease' either acute or chronic, or be just present as in carrier state<br>Hbs Ag thus indicated as possible:<br>- Acute disease<br>- Chronic disease<br>- Carrier state | With the development of antibody to Hbs Ag i.e. Anti Hbs Ag, the Hbs Ag antigen disappears from the serum<br>- Patient is immune (with immunization Antibody develops and Hbs Ag disappears)<br>- Patient is protected<br>Anti Hbs Ag indicates good immunity $^{Q}$<br>Anti Hbs Ag indicates protection against Hepatitis B $^{Q}$ |
| **Hbc Ag** | **Anti Hbc Ag** |
| It is a hidden component of the viral core and is not detectable at all | Antibodies to Hbc Ag develop early in the course of disease<br>Anti Hbc Ag is the first antibody to appear after an acute infection and persists in serum even during the recovery phase<br>- When acute antibody is of IgM type<br>- When chronic antibody is of IgG type |
| **Hbe Ag** | **Anti Hbe Ag** |
| Denotes high infectivity $^{Q}$ and active disease | Denotes low infectivity |

| Scheme of typical clinical and laboratory features of acute viral hepatitis B | Sequential |
|---|---|
|  | ***Hbs Ag***<br>↓<br>***Hbc Ag***<br>↓<br>***Anti Hbc Ag (IgM)***<br>↓<br>***Anti Hbc Ag***<br>↓<br>***disappearance of Hbs Ag and***<br>↓<br>***appearance of anti Hbs Ag.*** |

- ***After infection the first virological marker detectable in serum is – HBsAg$^{Q}$***

**Commonly Encountered Serologic Patterns of Hepatitis B Infection:**

| HBsAg | Anti-HBs | Anti-HBc | HBeAg | Anti-HBe | Interpretation |
|---|---|---|---|---|---|
| + | – | IgM | + | – | Acute hepatitis B, high infectivity |
| + | – | IgG | + | – | Chronic hepatitis B, high infectivity |
| + | – | IgG | – | + | Late acute or chronic hepatitis B,<br>Low infectivityHBeAg–negative ("precore–mutant") hepatitis B (chronic or, rarely, acute) |
| + | + | + | +/– | +/– | 1. HBsAg of one subtype and heterotypic anti–HBs (common)<br>2. Process of seroconversion from HBsAg to anti– HBs (rare) |
| – | – | IgM | +/– | +/– | 1. Acute hepatitis B<br>*2. Anti–HBc "window"* |
| – | – | IgG | – | +/– | 1. Low–level hepatitis B carrier<br>2. Hepatitis B in remote past |
| – | + | IgG | – | +/– | Recovery from hepatitis B |
| – | + | – | – | – | 1. Immunization with HBsAg (after vaccination)<br>2. Hepatitis B in the remote past (?)<br>3. False–positive |

- **Only marker detected in window period of Hepatitis B is IgM type Anti HBc**

*Presence of IgM Anti-HBc without HBs Ag may suggest acute hepatitis B in the window period.*

| HbsAg | Anti-HBs | Anti-HBc | HBeAg | Anti-HBe | Interpretation |
|---|---|---|---|---|---|
| + | - | ***IgM*** | + | - | Acute Hepatitis B, high infectivity |
| - | - | ***IgM*** | +/- | +/- | 1. Acute Hepatitis B<br>2. Anti—HBc "window" |

*Occasionally a gap of several weeks or longer may separate the disappearance of HBsAg and the appearance of Anti-HBs after an acute infection with Hepatitis B virus. During this 'gap' or 'window' period, presence of Anti-HBc may represent the only serological evidence of current or recent HBV infection*

- **The most reliable marker of acute HBV infection is IgM Anti HBc Antibody**

***Hbs Ag*** is present in recent hepatitis B infection but it ***is not specific to acute infection***
***IgM anti- HBc is specific for acute or recent hepatitis, and hence is the marker of choice for acute hepatitis B.***

*Although Hbs Ag is the earliest virological marker in serum of patients with acute viral hepatitis B; it does not help in establishing the diagnosis of acute Hepatitis B infection.This is so because presence of Hbs Ag only denotes the fact that the patient is a carrier of the above infection and such a patient may well be a case of chronic hepatitis B.*
*It is the presence of IgM anti HBc that confirms an acute hepatitis B infection.*
***Acute Hepatitis B is characteristically diagnosed by the presence of IgM anti HBc with HBs Ag.***
***Presence of IgM anti HBc without HBs Ag may suggest acute hepatitis in the window period.***

- **Vaccination or immunization against HBs Ag is suggested by Isolated Anti-HBs Ag in serum**

*Isolated Anti-HBs Ag in serum is seen in immunization with HBs Ag.*
*The marker for determining efficacy of hepatitis B vaccination is Anti – HBs Ag*

- **High Infectivity or active disease is indicated by HBeAg**

*The principal clinical usefulness ofHBe Ag is as an indicator of relative infectivity*

## Markers for Active Hepatitis B (Persistent Replication; High Infectivity: Active Disease)

**Markers for Active Hepatitis B**
*(Persistent Replication; High Infectivity: Active Disease)*

- *HBV DNA*
- *HBV DNA polymerase*
- *HBe Ag*

***AST & ALT levels are not considered markers for active viral replication***

***HBV DNA is the most sensitive marker of active Hepatitis B virus replication***

***HBV DNA$^{Q}$> HBV DNA polymerase$^{Q}$>HBeAg$^{Q}$***

### Markers for Hepatitis B Virus Replication

#### HBV DNA

- ***HBV DNA is the most sensitive and specific marker of virus replication***
- HBV DNA may provide both, a qualitative and quantitative estimate of virus replication
- *HBV DNA estimation as a measure of virus replication has largely replaced the determination of DNA polymerase*
- ***The Gold standard for confirmation of viral replication is HBV DNA detection***

#### HBV DNA Polymerase

- ***HBV DNA polymerase is considered the traditional marker active viral replication***
- HBV DNA polymerase activity usually parallel's serum HBV DNA levels
- Both HBV DNA and HBV DNA polymerase are markers for the complete virion.

#### HBe Ag levels

- ***HBeAg is considered a convenient and readily detectable qualitative marker of HBV replication and relative infectivity***

*The HBe Ag if detectable is considered a marker for active viral replication, but the lack of HBe Ag does not exclude viral replication*

### Markers for HBV Replication

#### Qualitative Markers

***HBe Ag** is a qualitative marker for HBV replication*

#### Quantitative Markers

- ***HBV DNA** is a quantitative definitive marker for HBV replication*
- ***DNA polymerase** is a definitive marker for HBV replication*

## Various Chronic Hepatitis B Categories

**Chronic Hepatitis B** *(HBs Ag + ve with IgG Anti HBc)*

Chronic Hepatitis B can be divided into two categories
Based on activity of the virus and evidence of liver damage

### Inactive HBs Ag Carrier state

- Patients with negligible virus replication (HBV DNA levels $\leq 10^3$virions/ml) and /or no clinical signs and symptoms of liver damage and normal liver enzyme levels are characterized as inactive HBV carriers
  *Inactive HBV carriers harbor Hepatitis B virus antigen (HBs Ag), but are clinically asymptomatic, have a normal physical examination with normal liver enzymes (AST & ALT). HBe Ag is typically negative and levels of HBV DNA are less than $10^3$-$10^4$virions/ml*
- Such patients have minimal (if any) liver inflammation or damage, and usually live a normal life. However compared to the general population these patients remain at risk for hepatocellular carcinoma
- Treatment is currently not recommended for Inactive HBV carrier. However *regular observation is advised* as there is a risk for reactivation of virus.

### Chronic Hepatitis B (Active)

- Patients with active virus replication (HBV DNA levels > $10^3$ -$10^4$virions/ml) and /or clinical signs and symptoms of liver damage or elevated liver enzyme levels are characterized as chronic hepatitis B patients.
- Depending on the presence or absence of HBe Ag two type of chronic (active) hepatitis B may be identified.

### HBe Ag positive chronic hepatitis B

*These HBs Ag positive, individuals are also positive for HBe Ag and show detectable HBV DNA levels. Such patients are in the replicative phase of chronic hepatitis B infection, have persistently or intermittently elevated liver enzymes and liver biopsy results typically reveals inflammation and damage*

Patients with chronic (active) hepatitis B may become inactive (relatively non replicative) over time (rate of ~10 % per year) by becoming negative for HBe Ag and HBV DNA (HBV DNA < $10^3$ - $10^4$) virions/ml) Liver injury tend to subside in such patients and these may then be characterized as 'inactive carriers'

### HBe Ag negative chronic hepatitis B (Precore mutant)

*Such HBs Ag positive individuals are negative for HBe Ag but show detectable HBV DNA levels. Such patients are also in the replicative phase of chronic hepatitis B (despite negative HBe Ag) and have persistently or intermittently elevated liver enzymes and liver biopsy results typically reveal severe inflammation and damage*

Negative HBe Ag Status *results from a mutant strain of hepatitis B that is characterized by the failure of the virus to make the hepatitis B 'e' antigen (HBe Ag)*. This mutation is called the ***'precore' mutation*** as it prevents the translation of a precore protein to prevent HBe antigen production.
*This mutation does not however affect the ability of the virus to replicate*

**Evidence of chronic active hepatitis B (suggested by elevated liver enzymes) in patients with detectable HBV DNA but negative HBe Ag suggests a diagnosis of precore mutant chronic hepatitis B**

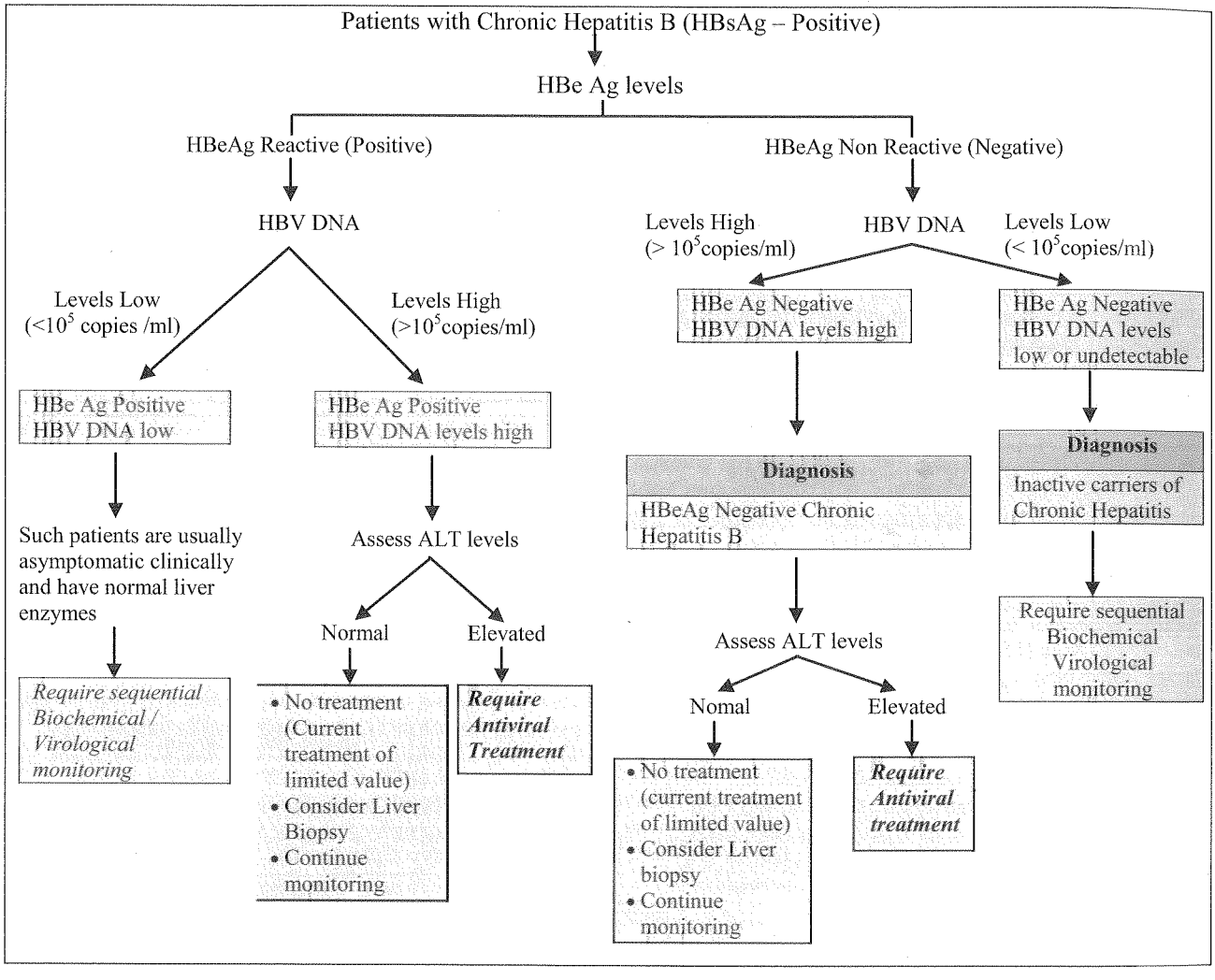
**Precore mutant form of chronic hepatitis B**

- Represents an infection with a molecular variant of the hepatitis B virus that results in an *unusual serologic – clinical profile.*
- ***Such patients have severe chronic hepatitis B infection with detectable HBV DNA levels, but HBe Ag antigen is typically negative***
- This *results from an infection with an HBV mutant that contains an alteration in the precore regions rendering the virus incapable of encoding HBe Ag*
- Patients with such mutations in the precore region are unable to secrete HBe Ag, have a negative HBe Ag phenotype but *tend to have severe liver disease that progresses more rapidly to cirrhosis*
- *Characteristic of such HBe Ag negative (precore mutant) chronic hepatitis B are lower levels of HBV DNA ($\leq 10^5$ copies /ml) and one of several patterns of aminotransferase activity – persistent elevation, periodic fluctuation above the normal range and periodic fluctuations between the normal and elevated range*
- *HBe Ag negative chronic hepatitis B with mutation in the pre-core region is now the most frequently encountered form of hepatitis B in the Mediterranean countries and in Europe.*

## Assessment of need for Antiviral therapy in Chronic Hepatitis B

*Antiviral therapy is indicated for patients with active HBV replication*
*Active HBV replication is best assessed by measuring serum HBe Ag levels and HBV DNA levels*

| Markers for Active HBV Replication |
|---|
| $HBeAg^{\varrho}$ |
| $HBV-DNA^{\varrho}$ |




**Seven drugs have been approved for treatment of chronic Hepatitis B (Harrisons)**

1. *Interferon α(and Pegylated Interferon)*
2. *Lamuvudine (oral)*
3. *Adefovir (oral)*
4. *Entecavir (oral)*
5. *Dipivoxil (oral)*
6. *Telbivudine*
7. *Tenofavir*

## Recommendations for Treatment of Chronic Hepatitis B

*Based on practice guidelines of the American Association for the Study of Liver Diseases (AASLD).*

| HBeAg status | Clinical | HBV DNA (IU/ml) | ALT | Recommendation |
|---|---|---|---|---|
| HBeAg-reactive | Mild or Inactive Liver disease | >2 x$10^4$ | ≤2 x ULN | No treatment; monitor. In patients >40, with family history of hepatocellular carcinoma, and/or ALT persistently at the high end of the twofold range, liver biopsy may help in decision to treat |
| | Chronic hepatitis | >2 x $10^4$ | >2 x ULN | Treat[e] |
| | Cirrhosis compensated | >2 x $10^3$ | <or> ULN | Treat[e] with oral agents, not PEG IFN |
| | | <2 x $10^3$ | >ULN | Consider treatment |
| | Cirrhosis decompensated | Detectable | <or> ULN | Treat[e] with oral agents[g], not PEG IFN; refer for liver transplantation |
| | | Undetectable | <or> ULN | Observe; refer for liver transplantation |
| HBeAg-negative | Mild or Inactive Liver disease | ≤2 x $10^3$ | ≤ULN | Inactive carrier; treatment not necessary |
| | Chronic hepatitis | >$10^3$ | 1->2 x ULN | Consider liver biopsy; treat[h] if biopsy shows moderate to severe inflammation or fibrosis |
| | Chronic hepatitis | >$10^4$ | >2 x ULN | Treat[h,i] |
| | Cirrhosis compensated | >2 x $10^3$ | <or> ULN | Treat[e] with oral agents, not PEG IFN |
| | | <2 x $10^3$ | >ULN | Consider treatment |
| | Cirrhosis decompensated | Detectable | <or> ULN | Treat[h] with oral agents[g], not PEG IFN; refer for liver transplantation |
| | | Undetectable | <or> ULN | Observe; refer for liver transplantation |

[e] One of the potent oral drugs with a high barrier to resistance (entecavir or tenofovir) or PEG IFN can be used as first-line therapy. These oral agents, but not PEG IFN, should be used for interferon-refractory/intolerant and immunocompromised patients. PEG IFN is administered weekly by subcutaneous injection for a year; the oral agents are administered daily for at least a year and continued indefinitely or until at least 6 months after HBeAgseroconversion.

[g] Because the emergence of resistance can lead to loss of antiviral benefit and further deterioration in decompensated cirrhosis, a low-resistance regimen is recommended-entecavir or tenofovirmonotherapy or combination therapy with the more resistance-prone lamivudine (or telbivudine) plus adefovir. Therapy should be instituted urgently.

[h] Because HBeAgseroconversion is not an option, the goal of therapy is to suppress HBV DNA and maintain a normal ALT. PEG IFN is administered by subcutaneous injection weekly for a year; caution is warranted in relying on a 6-month posttreatment interval to define a sustained response, because the majority of such responses are lost thereafter. Oral agents, entecavir or tenofovir, are administered daily, usually indefinitely or, until as very rarely occurs, virologic and biochemical responses are accompanied by HBsAgseroconversion.

[i] For older patients and those with advanced fibrosis, consider lowering the HBV DNA threshold to >2 x $10^3$ IU/ml.

***Abbreviations***: ULN, upper limits of normal;PEG IFN, pegylated interferon.

## Prognosis in HBV Infection

**Prognosis in HBV Infection**

*Acute HBV infection ≤ simultaneous HBV – HDV confection << HDV super-infection on HBV infection*

*(Best prognosis)* *(Worst prognosis)*

***Q HDV superinfection of a person with chronic Hepatitis B (HBV) has the worst prognosis with high likelihood of fulminant hepatitis and death***

## Glomerulonephritis associated with Hepatitis B

| Glomerulonephritis during chronic Hepatitis B infection |
|---|
| *Membranous Glomerulonephritis (MGN)* |
| *Membranoproliferative Glomerulonephritis (MPGN)* |
| *Mesanglocapillary glomerulonephritis* |

**Note**

*MGN is most commonly seen **in children**[Q]*
*MPGN is most commonly seen **in adults**[Q]*

# Hepatitis C

## Essential Features of Hepatitis C

- *HCV is the most common Virus associated with transfusion-associated hepatitis* Q
- *Themost common/prominent mode of transmission is through percutaneous route*
- *Hepatitis C does not spread through feco-oral route*
- *No vaccine / prophylaxis is available for HCV* Q
- *Malignant potential is present with HCV (also with HBV)* Q
- ***Hepatitis C is associated with Anti-LKM antibodies.***

**LKM antibodies** stand for antibodies against Liver-Kidney microsomes.

**LKM antibodies may be seen in**

- *Type II autoimmune hepatitis (anti LKM-I)*
- *Drug induced hepatitis (anti LKM-II)*
- *Chronic hepatitis C (Usually anti-LKM-I)*
- *Chronic hepatitis D (anti LKM-III)*

## Extrahepatic Manifestations of Hepatitis C

**Extrahepatic manifestations in viral hepatitis C:** *'Hepatology' by Kuntz*

- *Agranulocytosis*
- *Aplastic anaemia*
- *Corneal ulceration*
- *Cryoglobulinaemia*
- *Diabetes mellitus (type I)*
- *Erythema exsudativummultiforme*
- *Glomerulonephritis*
- *Guillain-Barre syndrome*
- *Hyperlipasaemia*
- *Lichen planus*
- *Non-Hodgkin lymphoma*
- *Polyarteritisnodosa*
- *Polyarthritis*
- *Polyneuritis*
- *Porphyria cutaneatarda*
- *Sialadenitis*
- *Sjogren's syndrome /Sicca syndrome*
- *Thrombocytopenia*
- *Thyroiditis*

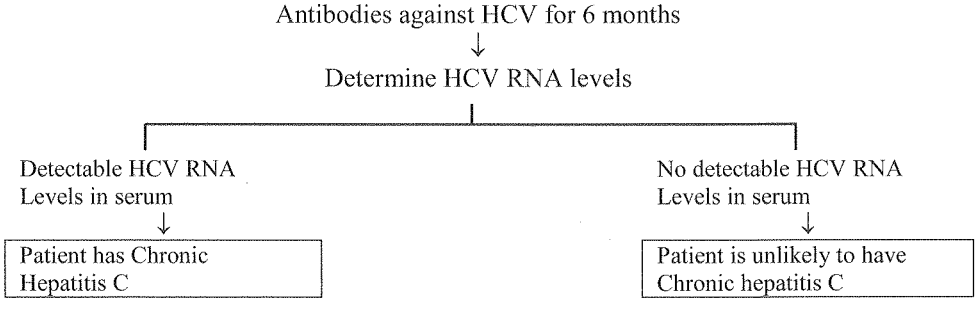
*Hepatitis C is also associated with* ***essential mixed cryoglobulinemia (EMC)*** *- Harrison 14th/1683*

Essential mixed cryoglobulinemia is an extrahepatic manifestation of viral hepatitis. It was reported initially to be associated with hepatitis B. Recent reevaluation of patients with EMC suggests that association is with chronic HCV infection rather than HBV infection.

## Diagnosis and Management of Chronic Hepatitis C

*Antibodies against HCV in the blood indicate infection with Hepatitis C virus.If the infection persists for more than 6 months and HCV RNA levels confirm viral replication, then the person can be confirmed as having chronic hepatitis C.*

***HCV RNA levels in the setting of elevated antibodies to HCV for 6 months determine serological diagnosis of chronic hepatitis.***




*Antibodies against HCV (anti- HCV) in the blood indicate infection with the HCV. Persistance of antibodies for 6 months suggests a diagnosis of chronic hepatitis C. Patients with chronic hepatitis C, even with normal ALT levels are candidates for Liver biopsy to establish a histo-pathological diagnosis of chronic hepatitis.* ***Patients with at least moderate grade and stage are candidates for antiviral therapy with PEG IFN and ribararin regardless of the ALT levels***

*'Although patients with persistantly normal ALT levels tend not to progress histologically, they respond to antiviral therapy just as well as do patients with elevated ALT levels. Such patients are potential candidates for antiviral therapy'*

*- Harrisons 17th/ 1965*

Persistence of Antibodies to HCV for > 6 months
+
Positive HCV RNA in serum
↓
Patient has Chronic Hepatitis C

| Elevated ALT | Normal ALT |
|---|---|
| ↓ | ↓ |
| *Treatment can be started without liver biopsy* | Perform Liver biopsy to obtain histological diagnosis and stage of chronic hepatitis |
| | ↓ |
| | *Evidence of chronic hepatitis on histopatholgy (at least moderate grade) is an indication for starting treatment (even in patients with normal ALT)* |

## Treatment of Choice for Chronic Hepatitis C

**Treatment of choice in Hepatitis C infection**

| Recommended treatment for hepatitis C | Recommended Retreatment for Relapsers or Non Responders |
|---|---|
| First line Treatment | First line treatment |
| Combination therapy with PEG – Interferon plusRibavarin<br>48 weeks of therapy for Genotypes I and 4<br>24 weeks of therapy for Genotypes 2 and 3 | Combination therapy with PEG – Interferon plus Ribavarin |

Chronic hepatitis C: 'Evidence Based medicine Guidelines' 1st (2005) / 330

- Increased serum ALT 6 months after the onset of symptoms: (normal ALT does not, however, rule out chronic hepatitis).
- A patient with a positive HCV-PCR-test and permanently elevated ALT most probably has a mild chronic hepatitis and treatment decisions can be made without liver biopsy in genotypes 2 and 3.
- Liver biopsy is indicated in a patient with positive HCV-PCR- test and normal ALT, and with genotypes 1 and 4 before considering therapy. Signs of chronic hepatitis in the biopsy are an indication for treatment.
- Information on the genotype of the virus is important to guide treatment decisions. Treatment is more effective for genotypes 2 or 3 than for genotypes 1 and 4.
- Treatment with a combination of interferon alpha or pegylated interferon alpha and ribavirin is used for 48 weeks for genotypes 1 and 4 and for 24 weeks for genotypes 2 and 3.
- When treating genotypes 1 or 4. If there is no response at 12 weeks (HCV-PCR still positive), the treatment is discontinued.
- Liver transplantation is indicated if the expected survival is about 6 months

## Prognostic Markers for response to antiviral therapy in the treamtment of chronic hepatitis C

**Reduced Responsiveness**

- ***Genotype 1***
- High levels of HCV RNA
- ***Adranced fibrosis (ciorrhosis, bridging fibrosis)***
- Long duration disease
- ***Age > 40 years***
- Immunosupression
- African American
- Obesity
- Hepatic steatosis
- Reduced adherence
- Male sex (*Handbook of Gastroenterology*)

**Sustained Responsiveness**

- Genotype 2 and 3
- Low levels of HCV RNA
- Minimal fibrosis
- Short duration disease
- Age < 40 years
- Immunocompetance

Others

- Absence of obesity
- Absence of Hepatic steatosis
- Increased Adherence
- Female sex (*Handbook of Gastroenterology*)

# Hepatitis E

**Essential Features of Hepatitis E**

- *Hepatitis E is synonymous with enterically transmitted non-A non-B Hepatitis*
- *Hepatitis E is transmitted only by fecooral route (Most common route of aquisition /transmission is fecoralroute*[Q]*)*
- *Hepatitis E is associated with increased mortality in pregnant females*
- *Hepatitis E is the Most common cause of Fulminant Hepatitis amongst pregnanatwomen*[Q]
- *Hepatitis E is the Most common cause of epidemic Hepatitis amongst adults in India*[Q]
- *Hepatitis E is the Most common cause of sporadic Hepatitis amongst adults in India*[Q]

Most common cause of ***sporadic cases in children is - Hepatitis A.*** [Q]

# Autoimmune Hepatitis

## Charachterisitic Features of Autoimmune Hepatitis

Characteristic Autoantibodies for Autoimmune Hepatitis

- *Antinuclear Antibodies (ANA)*
- *Anti LKM Antibodies (Anti- Liver-kidney microscomal antibodies)*
- *Anti- SLA (Antibodies against Soluble Liver Antigens)*
- *Anti- SMA (Antibodies against smooth muscle Antigens*

Autoimmune Hepatitis

| Type I | Type II | Type III |
|---|---|---|
| Characteristic Autoantibody profile<br>*ANA ++*<br>*SMA ++* | Characteristic Autoantibody Profile<br>***Anti LKM1 ++*** | Characteristic Auto antibody profile<br>***Anti – SLA ++***<br>***ANA +/- ; SMA +/-*** |
| Associated Antibody Profile<br>*P ANCA*<br>*Anti – Actin*<br>*Anti – ASGPR* | Associated Antibody Profile<br>*Anti- LC1*<br>*Anti – ASGPR* | Associated Antibody profile<br>*Anti – ASGPR* |

*ANA (Antinuclear Antibodies); anti- ASGPR (antibody to asialoglycoprotein receptor); anti LC1 (antibody to Liver cytosol type I); anti- LKM1 (antibody to soluble liver kidney microsome Type I); anti, SLA (antibody to soluble liver antigen). 'Autoimmune hepatitis has been recognized to recur in upto 40% of transplanted livers as immunosupression is reduced.' - CMDT' 2006 / 663*

**Autoimmune Hepatitis has a high incidence of recurrence after Liver Transplantation**

**Recurrance of primary disease following liver transplantation**

| Auto immune Hepatitis | Primary billary Cirrhosis | Wilson's disease Alpha$_1$ –Antitrypsin deficiency |
|---|---|---|
| Disease has been recognized to recur in upto 40% of transplanted livers as immunosupression is reduced *(CMDT)* | Disease recurs in the graft in 20% by 3 years' – *CMDT* | 'Hereditary disorders such as Wilson's disease and $\alpha_1$ antitrypsin deficiency have not recurred after liver transplantation' – *Harrisons 16/e, p 1878* |

# Alcoholic Hepatitis

## Feature of Alcoholic Hepatitis

**Feature of Alcoholic Hepatitis**

| Features suggesting Hepatocyte injury (Enzyme studies) | Features suggesting dearrangementinHepatocyte function |
|---|---|
| **AST/ALT**<br>• Levels are increased<br>• Increased is less than 8 fold (< 400u/L)<br>• AST is elevated greater than ALT<br>• AST: ALT Ratio >1<br>AST: ALT>2 is suggestive<br>AST: ALT>3 is highly suggestive | **Bilirubin**<br>• May be markedly elevated<br>• Both fractions (direct/indirect) may be elevated<br>**Albumin**<br>• Often decreased (Hypoalbuminemia)<br>• Albumin <2.5 mg/dlsuggests severe alcoholic hepatitis |
| **Alkaline Phosphatase**<br>• Levels are increased (may be normal)<br>• Increase is moderate (<3 times normal)<br>Normal to < 3 times normal elevation | **Prothrombintime**<br>• Often prolonged<br>• Fails to correct with parentralvitK(Coagulopathy) |
| **Gamma GlutamylTranspeptidase (GGT)**<br>• Levels are increased<br>• Note that GGT elevation is not specific to alcohol<br>GGT is easily inducible and may be elevated in all forms of fatty liver | Others<br>• *Polymorphonuclear cells (Neutrophils)* are often increased and if > 5500/µl predict severe alcoholic hepatitis.<br>• *Hypertriglyceredemia* and *Hypercholesterolemia* may be associated with alcoholic fatty liver. |

### Pattern of aminotranferases and etiology of hepatitis

| Alcoholic Hepatitis | Non Alcoholic Hepatitis (Viral/toxin induced) |
|---|---|
| • AST/ALT Ratio > 1 (>2 or >3 may be seen)<br>• AST/ALT elevation is moderate and rarely >400 u/L (Less than 8 fold increase)<br>• AST is elevated more than ALT | • AST/ALT ratio <1<br>• AST/ALT elevation is usually more marked and often >500 u/L (More than 8 fold increase)<br>• ALT is elevated more than AST |

*The low level of ALT in alcoholic liver disease is due to an alcohol-induced deficiency of pyridoxal Phosphate.*

*In alcoholic liver disease the AST rises out of proportion to ALT such that the ratio of AST and ALT may become greater than 2.*

| AST (SGOT) out of proportion to ALT (SGPT) seen in $^{Q}$ |
|---|
| 1. Alcoholic hepatitis $^{Q}$ |
| 2. Fatty liver in pregnancy $^{Q}$ |

### Stigmata of Alcoholic hepatitis / cirrhosis that aid in diagnosis:

1. *Bilateral enlarged parotids* $^{Q}$
2. *Gynaecomastia* $^{Q}$
3. *Testicular atrophy with loss of body hair* $^{Q}$
4. *Wasting of muscle mass* $^{Q}$
5. *Duputyrens contracture* $^{Q}$

$^{Q}$***Pentoxyfylline has shown to reduce mortality from renal failure in alcoholic hepatitis.***

# Non-Alcoholic Fatty Liver Disease (NAFLD/NASH)

## Causes of Non- Alcoholic Fatty Liver Disease (NAFLD) or Non-Alcoholic Steato-Hepatitis (NASH)

**Causes of Non-Alcoholic Fatty Liver Disease (NAFLD) or Non-Alcoholic Steato-Hepatitis (NASH)**

- *Obesity (present in > 40% cases)*
- *Diabetes mellitus (present in > 20% cases)*
- *Hypertriglyceredemia (>20%)*
- *Endocrinopathies (Cushing's and Hypopituitarism, PCOS)*
- *Metabolic disorders (Hyperbetalipoproteinemia)*
- *Obstructive sleep apnea*
- *Starvation and Refeeding syndrome*
- *Total parentral Nutrition*
- *Medications and poisons*
  *-Corticosteroids - diltiazem - irinotecan*
  *- Antiretroviral therapy, -Amiodarone- tamoxifen*
  *-Oxaliplatin - $CCl_4$& Yellow phosphorus*

Commonest **Associations of NAFLD / NASH** *(Robbins)*

- *Obesity*
- *Dyslipidemia*
- *Hyperinsulinemia (Insulin resistance is a charachteristicfeature[Q])*
- *Diabetes*

- *NAFL is now considered the most common cause of 'cryptogenic cirrhosis' – Robbins 7th/908*
- *Most patients with NAFLD come to medical attention as a result of incidentally elevated liver enzymes*
  - *ALT > AST*
  - *Aminotransferases are usually only mildly elevated 2 times normal*

## Treatment of NAFLD or NASH

**Treatment of NAFLD**

| Mainstay of treatment | Pharmacological Rx | Bariatric Surgery |
|---|---|---|
| Weight loss and exercise | **No drug with proven effuctiveness** | For associated morbid obesity |

**Drugs used to treat NASH**

| Insulin Sensitizing | *Antioxidants* | Hepatoprotectant | *Lipid lowering* |
|---|---|---|---|
| *Metformin* | *Vitamin E* | *Ursodeoxycholic acid* | *Statins* |
| *Pioglitazone* | *Betaine* | | *Gemfibrozil* |
| *Rosiglitazone* | | | |

# Cirrhosis and its Complications

## Morphological Classification of Cirrhosis

**Morphological ClassificationofCirrhosis**

| Macronodular Cirrhosis (Parenchymal nodules > 3mm) | | Micronodular Cirrhosis (Parenchymal nodules < 3mm) | |
|---|---|---|---|
| **Aetiology** | **Frequency** | **Aetiology** | **Frequency** |
| • *Chronic viral hepatitis* | *10-20%* | • *Alcohol* | *60-70%* |
| • *Wilson's disease* | *Rare* | • *'Primary' biliary cirrhosis* | *5%* |
| • *α-Antitrypain deficiency* | *Rare* | • *Large bile duct obstruction* | *<5%* |
| • *Various drugs and toxins* | *Rare* | • *Haemochromatosis* | *5%* |
| • *Hereditary haemorrhagic telangiectasis* | *Rare* | • *Intestinal bypass* | *Rare* |
| | | • *Cystic fibrosis* | *Rare* |
| • *Cryptogenic cirrhosis* | *Common* | • *Indian childhood cirrhosis* | *Rare* |

Q ***Postnecrotic cirrhosis is charachterized by a shrunken liver with reduced liver span.***

Q **In advanced stages of cirrhosis major blood supply to Liver is from hepatic artery**

Normally 80% of blood flow toliver comes from the portal vein and 20% of the blood supply is contributed by the hepatic artery

*In cirrhosis the blood flow to liver from the portal vein is reduced due to increased pressure and a compensatory increase in the blood to liver through the hepatic artery occurs*

## Stigmata of Chronic Liver Disease / Cirrhosis

**Stigmata of Chronic liver Disease**

| Cutaneous | Nails and Hands | Male sex organ | Features of portal hypertension |
|---|---|---|---|
| • *Spider angiomata (telangiectasias)* | • *Muchrcke's nails* | • *Gynecomastia* | • *Splenomegaly* |
| • *Palmar erythema* | • *Terry's nails* | • *Testicular atrophy* | • *Ascites* |
| • *Jaundice (ictreus)* | • *Clubbing and hyperthrophicosteoarthroplathy* | | • *Caput medusa* |
| • *Paper money skin* | • *Dupuytren's contracture* | | • *Cruveilhier-Baumgarten murmur* |
| | • *Drumstick fingers* | | • *Fetor hepaticus* |
| | | | • *Asterixis* |

## Portal Hypertension

- **Portal hypertension**refers to increased pressure in the portal vein and most commonly results from increased resistance to portal blood flow.

| Normal Pressure in the Portal Vein | |
|---|---|
| cm (Saline) | *10 – 15 cm saline* |
| mm (Hg) | *5 – 10 mmHg* |

- ***Portal hypertension in patients with cirrhosis most commonly results from increased resistance at the level of sinusoids***

**Increased resistance can occur at three levels:**

| Presinusoidal | Sinusoidal | Post sinusoidal |
|---|---|---|
| • Anatomically outside the liver eg. Portal vein thrombosis<br>• Within the liver but proximal to sinusoids eg. Schistosomiasis | ***Cirrhosis***<br>*When cirrhosis is complicated by portal hypertension, the increased resistance is usually sinusoidal* | • Outside liver, at level of hepatic veins<br>- ***Budd chiarri syndrome***<br>• In the inferior vena cava<br>- Thrombosis<br>• In the liver but distal to sinusoid<br>- Venoocclusive disease |

- Cirrhosis is the most common cause of portal hypertension in the United States.[Q]
  *Portal vein obstruction is the second most common cause.* [Q]
- *The most charachteristic features of Portal Hypertension are hematemesis from esophageal varices and splenomegaly*
  ***The most constant finding in patients with portal hypertension is splenomegaly (present in 80% of patients).-CSDT***
- ***Presence of massive haematemesis in the background of moderate splenomegaly suggests a diagnosis of esophageal varices secondary to portal hypertension.***

### Esophageal Varices

***Oesophagealvariceal bleeding secondary to portal hypertension should always be the initial diagnosis in a young patient presenting with massive hematemesis and a moderate to large splenomegaly'***

- *Most common presentation of esophageal varices is* ***Hematemesis which may be 'massive'***
  *Massive hematemesis in children is almost always due to variceal bleed – Shwartz*
- Presence of moderate splenomegaly is an important pointer towards presence of portal hypertension.
- The management of choice for variceal bleed is urgent endoscopy with ligation of the offending vessel

**Management protocol :**

Cardinal principles of resuscitation
(**A**irway / **B**reathing / **C**irculation)
↓
**Urgent endoscopy**
(diagnostic + therapeutic modality)
***Ligation is the endoscopic therapy of choice for variceal bleeding***
Endoscopic Sclerotherapy is another option
Acute treatment with octreotide (preferred over vasopressin) is the medical management of choice

**Principles :**

- Once the patient is hemodynamically stable urgent endoscopy should be performed
- Ligation is the endoscopic therapy of choice for esophageal varices because it has requires fewer treatment sessions.
- Endoscopic Sclerotherapy is another option
- Acute treatment with octreotide (preferred over vasopressin) is the medical management of choice
- In patients who have persistent or recurrent bleeding despite endoscopic and medical therapy, TIP is recommsended (TIPS is Transjugular intrahepatic portosystemic shunt)

# Ascitis

## Causes of Chylous and Mucinous Ascitis

ChylousAscitis refers to a turbid milky or creamy peritoneal fluid due to the presence of thoracic or intestinal lymph. It is most often a result of lymphatic obstruction from the cause mentioned below.

| Causes of ChylousAscitis |
|---|
| • Trauma |
| • Tumor |
| • Tuberculosis |
| • Filariasis |
| • Congenital anomalies |
| • Nephrotic syndrome |

| Causes of Mucinous Ascitis |
|---|
| • Pseudomyxomaperitonei |
| • Colloid carcinoma stomach with peritoneal implants |
| • Colloid carcinoma colon with peritoneal implants |
| *Colloid carcinoma of stomach causes mucinous ascities – Harrisons* |

**Treatment of Ascitis:**

Treatment of Ascitis: Oxford Textbook of Medicine: Recommendations

- ***Bed Rest*** *is of little value*
- ***Dietry sodium Restriction*** *is the first line management*
- ***Diuretic therapy*** *is the mainstay of treatment of Ascitis (Spironolactone should be employed as the* ***first line drug)***
- ***Large volume paracentesis****should initially be carried out on patients with moderate or marked ascitis*

  **Large volume Therapeutic Paracentesis is not recommended for SBP**
  *Diagnostic paracentesis is indicated in SBP for establishing the diagnosis but large volume paracentesis should be avoided - Schiff's Diseases of the Liver*
- ***Shunts (TIPS)*** *may be used in cases of Refractory Ascitis in whom recurrent paracentesis is too frequent or poorly tolerated, or in those with a hepatic hydrothorax*

**Q Abdominal ultrasound may detect as little as 100 ml of ascitic fluid**
*Ultrasound is thus a useful investigation for the diagnosis of minimal ascitis – CCDT*

**Q HemorrhagicAscitis is diagnosed when RBC count >10, 000 / $mm^3$**
*An RBC count of 10,000 / $mm^3$ is the threshold for pink appearance and hemorrhagic ascitis is thus diagnosed when ascitic RBC count is > 10,000 / $mm^3$ - Schiff's diseases of the Liver*

**Q Spontaneous Bacterial peritonitis (SBP) is diagnosed when Neutrophil count > 250/$mm^3$**
*The diagnosis of SBP is made when the absolute neutrophil count > 250 / mm3 – Harrisons*

## Primary Biliary Cirrhosis

Primary biliary cirrhosis is a disease characterized by chronic inflammation and fibrous obliteration of intrahepatic bile ductules due to an unknown (primary) stimulus.

**Etiology / pathogenesis :**

PBC is believed to be due to an autoimmune [Q] etiology as it is often associated with other autoimmune disorders [Q] such as

1. CREST [Q] :**C**alcinosis, **R**aynaud's, **E**sophageal dysmotility, SclorodactylyTalenglectasia
2. SICCA SYNDROME [Q]
3. Autoimmune thyroiditis [Q]
4. Renal tubular acidosis

- Antimitochondrial Antibody (IgG) is positive

**Clinical feature :**

- Most patients are asymptomatic [Q]
- Pruritis is commonest / earliest symptom [Q]

> ***'The earliest symptom is 'pruiritis' which may be either generalized or limited initially to the plams and soles.'*** - Harrison

- Jaundice [Q]
- Melanosis: gradual darkening of exposed areas of skin [Q]
- Deficiency of fat soluble vitamins due to malabsorption [Q]
  - Vit D deficiency : bone pain - osteomalacia [Q]
  - Vit K deficiency : bleeding – bruising [Q]
  - Vit A deficiency : Night blindness [Q]
- *Xanthelisman&xanthomas* [Q] due to protracted elevaliar of serum lipids.

**Lab Findings :**

- ↑↑ Serum alkaline phosphatase [Q] (2-5 fold)
- ***Positive antimitochondrialantibody***: [Q]Sensitive and specific
  *Antimitochondrial' Antibodies (AMA) are present in about 90% of patients with PBC' – Harrison*
- ***Hyperlipidemia (Abnormal Lipoprotein)***
  *'The serum levels of cholesterol increase strikingly in PBC and an abnormal lipoprotein (Lipoprotein- x) appears which is found in many forms of chronic cholestasis' – Rubin's pathology*

## Primary Sclerosing Cholangitis

### Primary SclerosingCholongitis

Progressive Idiopathic obliteration of intrahepatic or extrahepatic bile ducts

**Note**

*Smoking is associated with a decreased risk of PSC*

| Conditions with decreased risk from smoking |
|---|
| • *Ulcerative Colitis* |
| • *Primary biliary sclerosis* |

- *Most common in Men aged 20- 50 years (M > F)* [Q]
- *Characteristically associated with ulcerative colitis (IBD)* [Q] *(and less commonly with crohn's disease)*
- *Characteristic increased risk of cholangiocarcinoma (10%)*

| Presentation | Characteristic LaboratoryFeature | Diagnostic study of choice |
|---|---|---|
| • **Progressive obstructive jaundice.** Patient presents with progressive jaundice, pruiritis and other features of cholestasis | • **GGT is typically elevated** ***Asymptomatic elevation of GGT is the earliest finding*** • **ALP & bile acids are ↑ed** | *ERCP or MRCP is the diagnostic study of choice demonstrating irregularities of the biliary tree* |

***'The ultimate treatment of PSC is Liver transplantation' – Harrison***

## Non-Cirrhotic Portal Hypertension (NCPF and EHPVO)

- ***Non-Cirrhotic Portal Hypertension is charachterized by features of portal hypertension along with a moderate/large splenomegaly with conspicuous absence of features of liver cell failure***
- **Non-cirrhotic portal hypertension** encompasses two distinct pathological condition that present with similar clinical features.

| |
|---|
| Non cirrhotic portal fibrosis<br>Extrahepatic portal obstruction |

- *Signs of Liver failure such as Jaundice and Ascitis are uncommon in EHPVO and NCPF. Their presence favors a diagnosis of cirrhosis and their absence makes cirrhosis unlikely*

| **Non Cirrhotic Portal Hypertension is suspected in a patient presenting with symptoms of portal hypertension with:** |
|---|
| • Moderate/Large Splenomegaly<br>• *NO*FEATURES SUGGESTIVE OF LIVER CELL FAILURE<br>- No Jaundice (uncommon)<br>- No Ascitis (uncommon)<br>- No Hepatomegaly (uncommon)<br>- No Stigmata of liver cell failure (uncommon) |

- *Distinction between the two conditions should ideally be made by further investigations as the similarly in presentation makes clinical criteria unreliable.*
  *Neverthless if we do have to choose one single best option the following clues may be helpful.*

| Features | EHPVO | NCPF |
|---|---|---|
| • Defination | ***Extra-hepatic portal vein obstruction*** *refers to features of portal hypertension resulting from an extrahepatic block to the portsl venous system either from congenital malformations or acquired causes like thrombosis* | ***Non-cirrhotic portal fibrosis*** *is a condition of liver characterized by widespread fibrosis of the liver (mainly portal, subcapsular and rarely perisinusuoidal) causing wide variation in the normal architecture but there is no true cirrhosis.* |
| • ***Age*** | ***Children (1st & 2nd decade)***<br>*EHPVO may present in two age groups*<br>*Children(1st & 2nd decade)*<br>*(Congenital malformations)*<br>*Adults (4th & 5th decade)*<br>*(Thrombotic event)* | *Adults (3rd & 4th decade)*<br>*NCPF presents in young adults most commonly during the third and fourth decade* |
| • ***Gender*** | ***M > F*** | *F > M*<br>*NCPF is more common in females* |
| • Onset | *The onset of symptoms is gradual* | *The onset is gradual in children where the cause is congenital malformation*<br>*The onset is acute in adults where the cause is usually a thrombotic even* |
| • ***Splenomegaly***<br>***(Mass in Left upper quadrant)*** | ***Mild /Moderate***<br>*Mass in left upper quadrant (splenomegaly) is four times less common in patients with EHPH* | ***Moderate / Large***<br>*Mass in left upper quadrant (splenomegaly) is about 4 times more common in NCPF than EHPH* |
| • Variceal bleed (Hemetemesis / Malena) | + + | + + |
| • Jaundice / Ascitis Encephalopathy | *± (Absent / Transient)* | *± (Absent / Transient)* |
| • LFT | *Normal* | *Normal* |
| • Site of block along portal venous system | *Large branches are thrombosed (Main trunk; 1st order branches)* | *Small branches are involved (3rd order and 4th order branches)* |
| • USG | *Portal / Splenic vein block*<br>*'Portal covernoma'* | *Normal splenoportal axis* |

## Most common cause of Portal Hypertension in India

| Portal Hypertension in Indian Children | Portal Hypertension in Indian Young Adults |
|---|---|
| *The most common cause of Portal Hypertension in Indian Children is EHPVO* | *The most common cause of Portal Hypertension in Indian Adults is NCPF* |
| *NCPF is the most important causes of intrahepatic non-cirrhotic portal hypertension in India.* Q | |

*'More than three quarters of Indian Children with portal hypertension were found to have extra hepatic portal vein obstruction (EHPVO) and Indian studies have shownextra hepatic portal vein obstruction (EHPVO) to be the commonest non cirrhotic cause for portal hypertension in children'*

*- 'Diseases of the Liver and Biliary System in Children' by Kelly 3rd /559*

## Clinical Differentiation of NCPF, EHPVO and Cirrhosis in patients with features of Portal Hypertension

| Parameter | EHPVO | NCPF | Cirrhosis |
|---|---|---|---|
| Mean age (years) | 10 | 28 | 40 |
| Ascites | Absent/transient after bleed | Absent/transient after bleed | + to +++ |
| Encephalopathy | - | - | + |
| Jaundice signs of liver failure | - | - | + |
| Liver function tests | Normal* | Normal | Deranged |
| Liver<br>Gross<br>Microscopic | <br>Normal/small<br>Normal | <br>Normal, rarely irregular<br>Normal portal/fibrosis | <br>Shrunken, nodular<br>Necrosis, regeneration |
| Splenoportovenography/US | Portal/splenic vein block | Normal splenoportal axis, 'withered tree' appearance, periportal fibrosis | Dilated, patent portal and splenic vein |

*Occasional impairment may be observed
NCPF, non-cirrhotic portal fibrosis; EHPVO, extrahepatic portal vein obstruction; US, ultrasound

## Etiology of NCPF

- The precise etiology of NCPF remains an enigma.
- Infection, Chemicals and Immune mechanisms have all been implicated

INFECTION
– E. coli?
– Malaria?

Chemicals
– Arsenic Q
– Vinyl chloride Q

Immune mechanisms

↓

Features of portal hypertension
- Gastrointestinal haemorrhage (most common symptom)
- Lump in abdomen (enlarged spleen)
- Splenomegaly is common (massive)

**The implicated chemical agents include:**
- ***Arsenic***
- Copper
- Vinyl chloride

*"Chronic ingestion of Arsenic has been incriminated in causation of NCPF. High Hepatic arsenic levels in patients with NCPF have been reported" – API 7th/ 621*

**Arsenic in also associated with the following cancers** Q
1. Skin cancer Q (Chandrasoma Taylor 3rd/ 285)
2. Lung cancer Q (Chandrasoma Taylor 3rd/ 285)
3. Hepatic angiosarcoma Q (Chandrasoma Taylor 3rd/ 185)

# Hepatic Encephalopathy / Hepatic failure

## Common precipitants of Hepatic Encephalopathy

| Increased nitrogen load as in | Electrolyte and Metabolic imbalance such as in |
|---|---|
| 1. *GI bleeding* Q | 1. *Hypokalemia* Q |
| 2. *Excessive dietary protein intake* Q | 2. *Alkalosis* Q |
| 3. *Azotemia* Q | 3. *Hypoxia* Q |
| 4. *Constipation* Q | 4. *Hyponatremia* Q |
| **Drugs** | **Miscellaneous conditions like** |
| CNS depressant agents like narcotics, tranquillizers, sedatives Q | Infection Q, surgery Q, superimposed acute liver disease. Q |

***Anaemia*** may lead to cellular hypoxia at the level of liver cells and thus precipitates encephalopathy Q

***Hypothyroidism***, though not mentioned as a direct precipitating factor, may contribute towards precipitating encephalopathy by causing *'constipation'* or slowing down the intellectual and motor activity.

## Initial Laboratory abnormalities and Prognostic Factors in Hepatocellular Failure

- ***Patients with early hepatocellular failure may present with isolated prolongation of Prothrombin Time (PT)***

  *An increased prothrombin time is the most frequently observed first laboratory test suggesting the possibility of hepatocellular failure. Early liver failure may be suspected based on isolated prolongation of the Prothrombin Time (PT).*

- ***Prolonged Prothrombin Time and Factor V levels are important prognostic Factors***

| Coagulation factors as Laboratory Prognostic markers in patients with acute liver failure include the following: |
|---|
| 1. *Prothrombin time (King's criteria)* |
| 2. *Factor V levels (Clinchy's criteria)* |
| 3. INR (CMDT) |

*'The standard liver blood tests (AST, ALT, ALP, Bilirubin, Ammonia) have no discriminatory value affecting survival The extent to which plasma levels of liver derived coagulation factors are depressed correlates with the severity of the hepatic lesion.'*

## Diagnostic Criteria for Hepatic Encephalopathy

| The diagnosis of hepatic encephalopathy should be considered when four major factors are present |
|---|
| 1. Acute or chronic hepatocellular disease and/or extensive portal systemic collateral shunts |
| 2. Disturbance of awareness and mentation, which may progress from forgetfulness and confusion to stupor and finally coma. |
| 3. Shifting combinations of neurological signs including asterixis, rigidity, hyperreflexia, extensor plantar signs and rarely seizures. |
| 4. ***A characteristic but (nonspecific), symmetric, high voltage, triphasic slow wave (2 or 5/second) pattern on electroencephalogram.*** |

## Typical Causes of Flapping Tremors

*Asterexis (Flapping tremor) is most commonly seen in metabolic encephalopathies due to hepatic, renal (uremia) and respiratory failure ($CO_2$Nercosis).*

| Typical Metabolic Encephalopathies | |
|---|---|
| • ***Hepatic Encephalopathy*** | *Typically Metabolic Encephalopathies due to hepatic, renal and respiratory failure are the most common causes.* |
| • ***Uremic Encephalopathy*** | |
| • ***Respiratory failure with $CO_2$ Retention ($CO_2$ Narcosis)*** | |

*'Thyrotoxicosis (Hyperthyroidism) is associated with rapid fine tremors and not flapping tremors (irregular coarse tremor) also called Asterixis.*

## Hepatorenal syndrome

- Hepatorenal syndrome is defined as a state of functional renal failure (Reduced GFR) in patients with severe liver disease
- ***Structurally /Histologically the kidneys are normal and recover function after successful liver transplantation.***
- The pathogenetic hallmark of hepatorenal syndrome is intense renal vasoconstriction with coexistent systemic vasodilatation
- The diagnosis of hepatorenal syndrome is considered in accordance with the following diagnostic criteria.

| **Diagnostic of Hepatorenal Syndrome** |
|---|
| **Major criteria** |
| • *Low glomerular filtration rate, as indicated by serum creatinine> 1.5 mg/dL or 24-hr creatinine clearance < 40 mL/min* |
| • *Absence of shock, ongoing bacterial infection, fluid losses, and current treatment with nephrotoxic drugs* |
| • *No sustained improvement in renal function (decrease in serum creatinine to 1.5 mg/dL or increase in creatinine clearance to 40 mL/min) after diuretic withdrawal and expansion of plasma volume with 1.5L of a plasma expander* |
| • *Proteinuria <500 mg/dL and no ultrasonographic evidence of obstructive uropathy or parenchymal renal disease* |
| **Additional criteria** |
| • *Urine volume < 500 mL/d* |
| • *Urine sodium < 10 meq/L* |
| • *Urine osmolality greater than plasma osmolality* |
| • *Urine red blood cells <50/high- power field* |
| • *Serum sodium concentration < 130 mEqL* |
| Note: All major criteria must be present for the diagnosis of hepatorenal syndrome. Additional criteria are not necessary for the diagnosis but provide supportive evidence. |

# Hepatocellular Carcinoma

## Risk factors for hepatocellular carcinoma:

| **Major etiological factors** - *Robbins* | **Other etiological factors** – *Harrison* |
|---|---|
| • Viral infection<br>*Hepatitis C infection*<br>*Hepatitis B infection*<br>• Chronic alcoholism<br>• Food contaminants: Alfatoxins | • Alphal antitrypsin deficiency<br>• Hemochromatosis<br>• Tyrosinemia<br>• Primary biliary cirrhosis<br>• Exposure to thoriumdioxide or vinyl chloride<br>• Long term androgenic steroid administration<br>• Exposure to estrogen |

## Hepatocellular Carcinoma: Epidemiological Characterisitcs and Clinical Features

Hepatocellular Carcinoma

**Epidemiological Characteristics**
Mean Age > 50 years
Male: Female = 3:1

**Predisposing Factors (common)**
*Cirrhosis from any cause*
*Chronic Hep.B or Hep. C infection*
*Chronic Ethanol consumption*
*Non Alcoholic Steatohepatitis (NASH)*
*Aflatoxin B.*

**Symptoms**
- *Abdominal pain is the most frequent presenting symptom*[Q]

Other Symptoms
- Abdominal swelling
  - Mass
  - Ascitis
- Weight loss
- Loss of Appetite
- Weakness/Malaise

Rare Symptoms (uncommon)
- *Jaundice is rare in Hepatocellular CA*[Q]

**Tumor Markers**
***Alpha-fetoprotein levels are characteristically elevated.***

**Signs**
- ***Hepatomegaly is the most common physical sign occurring in 50-90% of patients***

Other Signs
- Ascitis (20%)
- Abdominal brui of Friction rub over liver
- Fever
- Signs of chronic liver disease
- Budd Chiari syndrome

**Most common clinical manifestations of hepatocellular carcinoma:**
- Abdominal pain and Abdominal Liver mass
  The most common presenting features are abdominal pain with detection of an abdominal mass in the right upper quadrant

**Uncommon / inconstant features**
- Jaundice: Jaundice is ***rare***, unless significant deterioration of liver function or mechanical obstruction of bile duct occurs
- Esophageal variceal bleeding: Gastrointestinal or esophageal variceal bleeding are ***inconstant*** findings

## Characteristic features of fibrolamellar carcinoma

**Characteristic features of fibrolamellar carcinoma**
- Distinctive variant of Hepatocellular carcinoma
- Occurs in young adults (20 to 40 years of age)
- *Equal sex incidence (Robbins); More common in females -Chandrasoma Taylor*
- No association with HBV or cirrhosis
- Well circumscribed mass (localized)
  *Non encapsulated but well circumscribed – Harrison*
  *Grossly encapsulated – Chandrasoma Taylor*
- ***No AFP elevation*** *-Chandrasoma Taylor*
- Better prognosis: Slow growth and longer survival.

***Hepatoblastoma*** ***is a malignant liver tumor of infancy i.e. typically associated with very high serum AFP levels.*** *The lesions are usually solitary, may be resectable and have a better five year survival than that of HCC.*

# Disorders of Biliary Tract

## Factors favouring the formation of Bile stones

Bile salts and phospholipids in bile keep cholesterol in solution by the formation of micelles.
An *excess of cholesterol relative to bite salts* ***and phospholipids*** allows cholesterol to form crystals and such bile is called *Lithogenic or Super-saturated bile.*

**Factors favouring the formation of Bile stones**

*Obesity* Q
*Clofibrate therapy* Q
*Age* Q
*Women on contraceptive* Q

↓
Increased Cholesterol

*Estrogen* Q
Interruption of enterohepatic circulation
- *Ilial disease* Q
- *Resection bypass* Q
- *Cholestyramine therapy* Q

↓
Decreased bile salts in circulation

↓
Lithogenic Bile
*Precipitation of cholesterol crystals 'Cholesterol stones'*

*It is increased concentration of cholesterol relative to bile salts in bile that promotes gall stone formation. Serum cholesterol may well be normal.*

- ***Diabetes mellitus*** *is associated with Gall bladder hypomotility, which may contribute to increased incidence of gallstone in diabetics.*

- ***Clofibrate therapy****: This drug is used to excrete cholesterol in hyperlipoprotenemialt therefore increases the concentration of cholesterol in bile.*
- ***Hyperalimentation:*** *Parental supplementation leads to hypofunction of Gall bladder, thus contibuting to gall stone formation by 'Stasis'.*
- ***Primary biliary cirrhosis:*** *Leads to a decrease in bile acid secretions. Decreased salts are unable to keep cholesterol in solution and therefore lead to precipitation of cholesterol stones*
- ***Truncal vagotomy****(not vagal stimulation) enhances Stone formation*
  *Vagotomy promotes stasis of bile by inhibiting gall bladder contractility and promotes stone formation.*
- ***Ileal resection is an established factor for gall stone formation.***
  *Ileal resection is associated with interruption of enterohepatic circulation of bile salts thereby decreasing the ratio of bile salts to cholesterol within the bile (Lithogenic bile)*

- *Cholelithiasis is more common in women than men*
- *The most common site of obstruction due to gallstone is the terminal ileum.*

| | |
|---|---|
| *'Classically there is obstruction / impaction about 60 cm proximal to ileocaecal valve'- Bailey* | *'The site of obstruction by the impacted gallstone is usually at the ileocaecal valve" provided that the more proximal S.I. is of normal calibre. - Harrisons* |
| *If both choices come simultaneously in a question go for 60 cm proximal to ileacoecal valve, as, it has been defined as the narrowest part of small intestine.* | |

- *The most common site of Biliary – enteric fistulas is the duodenum (Cholecystoduodenal fistula)*

| Type of fistula | Percent | Comment |
|---|---|---|
| *Cholecystoduodenal* | *≈75%* | *Most common type (duodenum)* |
| *Cholecysto colic* | *≈16%* | *Second most common (colon)* |

- *Medical therapy for gall bladder stone is amenable for stones < 15 mm (preferably <10 mm)*

**Prerequisitesfor medical therapy:**

1. *Gall bladder should be functioning* Q
2. *Stones should be radioluscent* Q
3. *Size should be small preferably <10-15 mm* Q *(<10mm-Harrison)*
4. *Stones should be 'cholesterol stones' only (obvious by thier mechanism of action)* Q

| Medical therapy for Gall stone dissolution | Mechanism of action: |
|---|---|
| *UDCA (Ursodeoxycholic acid)* Q<br>*CDCA (Choledeoxycholic acid)* Q | *Inhibit HmG CoA reductase activity* Q*, which in turn results in decreased hepatic cholesterol synthesis.Allows dispersion of 'cholesterol' from stones by physicochemical means.* |

- *Prophylactic cholecystectomy is not warranted in an asymptomatic patient.*

## Saint's Triad and Charcot's Triad

| Saint's triad (Association of) |
|---|
| *Diverticular disease* |
| *Gall stone/Cholelithiasis* |
| *Hiatus Hernia* |

| Charcot's triad |
|---|
| *Abdominal pain* |
| *High fever with rigors* |
| *Jaundice* |

## Predisposing factors of cholangiocarcinoma

***The predisposing factors of cholangiocarcinomainclude :***

1. Chronic hepato-biliary parasite infection Q
   (Clonorchiasis or Asiatic cholangio-hepatitis) Q
2. Congenital Anomaly with ectatic ducts (Choledochal cyst). Q
3. Sclerosing cholangitis Q
4. Ulcerative colitis Q
5. Occupational exposure to carcinogens Q
   (Rubber + Automotive plants)

- *Cholelithiasis is not clearly a predisposing factor for Cholangiocarcinoma– Harrison*
- *Chronic pancreatitis does not predispose to cholangiocarcinoma*

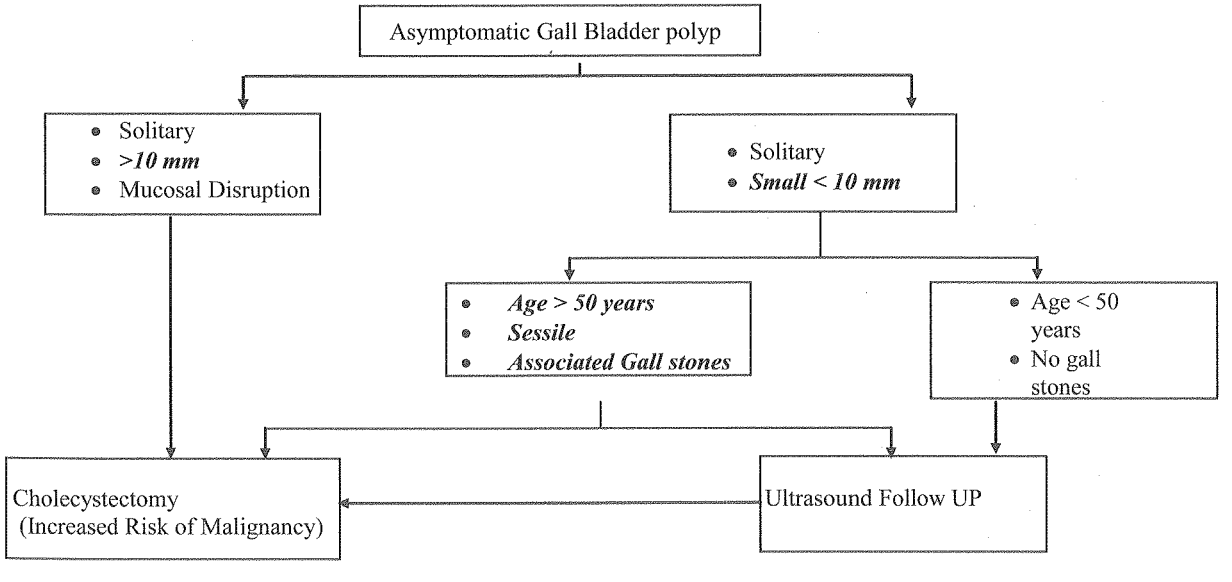
*Nodular lesions that arise at the bifurcation of hepatic ducts are called **Klastskin tumors**.* Q

## Factors, which indicate possibility of malignancy in Gall bladder Polyps

**Factors which indicate possibility of malignancy in Gall bladder Polyps**

- *Age > 50 years*Q
- *Sessile Polyps*Q
- *Rapid change in size of polyp*Q
- *Presence of a single polyp*Q
- *Polyp > 1.0 cm in size*Q
- *Associated Gall stones*Q

## Management Protocol for Asymptomatic Gall Bladder Polyps



## Causes of air in biliary tract

| Air coming from GI tract through fistulas caused by | Air Produced with in Biliary tract | Air coming from GI tract d/t failure of closure of sphincter of oddi/t reflux of duodenal gas |
|---|---|---|
| • Trauma<br>• Surgery<br>• ***Malignancy***[Q]<br>• Duodenal Ulcer<br>• ***Gall stone ileus***[Q] | • *Emphysematous cholecystitis*[Q] | • Passage of Stone<br>• Passage of Ascaris (Biliary ascariasis)<br>• Surgery (endoscopic sphincterotomy, sphincteroplasty, ***papillotomy***) |

[Q]***Sclerosing cholangitis is not associated with air in the biliary tract***

## Budd Chiari Syndrome:

- ***Budd chiari syndrome by definition is 'occlusion of hepatic vein'***
  *Budd chiari syndrome is characterized by post sinusoidal obstruction outside the liver at the level of hepatic veins*
- It is a clinical complex characterized by -
  - *Liver enlargement (hepatomegaly)*
  - *Ascitis*
  - *Abdominal pain*
- It is produced as a result of obstruction of two or more major hepatic veins and results from increased intrahepatic blood pressure and an inability of the massive hepatic blood from to shunt around the blocked outflow tract
  - *Obstruction of two or more major hepatic veins produces Budd chiari syndrome*
  - *Obstruction of a single main hepatic vein by thrombosis is clinically silent*
- The most common cause of Hepatic vein obstruction producing Budd chiari syndrome is Hepatic Vein Thrombosis.
  *The most common cause of Hepatic Vein Thrombosis causing Budd Chairi Syndrome is Polycythemia Vera*

**Hepatic vein thrombosis is associated with in decreasing order of frequency:** *Robbins*

- *Polycythemia vera*[Q]
- *Pregnancy*
- *Postpartum state*
- *Use of oral contraceptives*
- *Paroxysmal nocturnal hemoglobinuria (PNH)* [Q]
- *Intraabdominal cancers, particularly hepatocellular carcinoma.*

*It may also result from occlusion of IVC such as invasion by a tumour but this is certainly less common.*
*Idiopathic membranous obstruction of IVC is the most common cause of this syndrome in Japan*

## Wilson's Disease

*The basic defect in Wilson's disease is reduced biliary excretion of copper* due to a mutation of gene on chromosome 13, which promotes copper excretion. This leads to accumulation of copper initially in the liver and subsequently in plasma and other systems once liver is saturated. *Serum ceruloplasmin is the main copper binding protein in the blood and once excess copper spills into the blood,* ***levels of free ceruloplasmin are decreased.*** *Also excess copper is eventually excreted in urine and hence* ***urinary copper levels are increased or high.***

**Wilson's disease**

*Basic defect is Reduced biliary excretion of Cu*

(Mutation of gene on chromosome 13 which promotes Cu excretion)

↓ (*Autosomal recessive*) (ATP 7B gene)

***Accumulation of Cu in Hepatocytes***

*Coombs negative hemolytic anemia*[Q] is seen
*Renal tubular acidosis*[Q], though rare, may be seen

*All form of hepatitis* (including fulminant type)
- Acute hepatitis
- Fulminant hepatitis
- ***Chronic active hepatitis***
- Cirrhosis

Cu saturates liver, spills in plasma and is spread to other systems
(***Serum Ceruloplasmin is*** ↓↓[Q])

| CNS | Eyes | Genital | Kidney | Psychiatric changes |
|---|---|---|---|---|
| ***Deposits in Basal Ganglia*** [Q]<br>Neurological manifestations<br>- *Tremors: resting / intention* [Q]<br>- Spasticity / Rigidity<br>- *Chorea* [Q]<br>- Drooling/Dysphagia/Dysarthria<br>**Sensory Changes Never Occur** | ***Copper gets deposited in Descemet's*** [Q] ***membrane of cornea*** [Q]<br>*'Kayser*[Q]*Fleischner' ring* (KF rings do not interfere with vision) [Q]<br>*Sunflower cataract* [Q] | - Free copper in intrauterine secretions<br>- Primary or Secondary Amenorrhea [Q]<br>- Recurrent abortions [Q] | - Microscopic Hematuria,<br>- Nephrocalcinosis<br>- Renal calculi | - Loss of emotional control,<br>- Depression,<br>- Hyperactivity,<br>- Loss of sexual activity. |

### Kayser – Fleischer Rings (KF Rings) and Wilson's disease

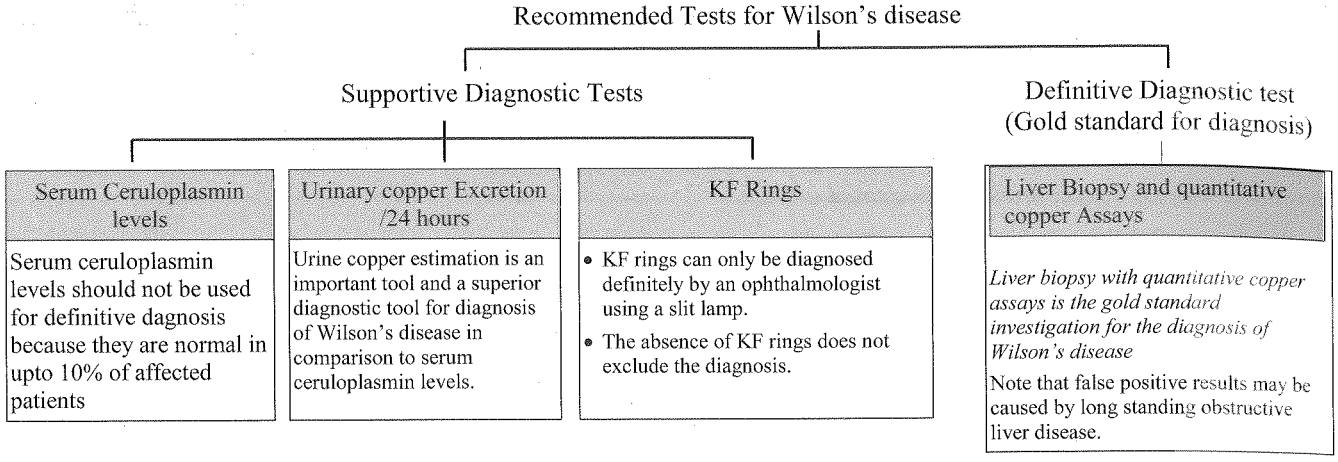
**Kayser – Fleischer Rings (KF Rings)**

- *Brownish yellow discolourations*[Q] *seen in limbic zone of cornea*
- *Result from deposition of copper in Descemet'smembrane*[Q] *of the cornea*
- *Do not interfere with vision*[Q]
- *Charachteristically seen in Wilson's disease*[Q] *but are not pathognomic*[Q] *of Wilson's disease* and may be seen in other conditions

| Conditions that may present with KF rings |
|---|
| • ***Wilson's disease (characteristic***[Q]***)*** |
| • *Chronic Active Hepatitis / Autoimmune Hepatitis* |
| • *Primary Biliary Cirrhosis* |
| • *Intrahepatic cholestatic syndromes* |

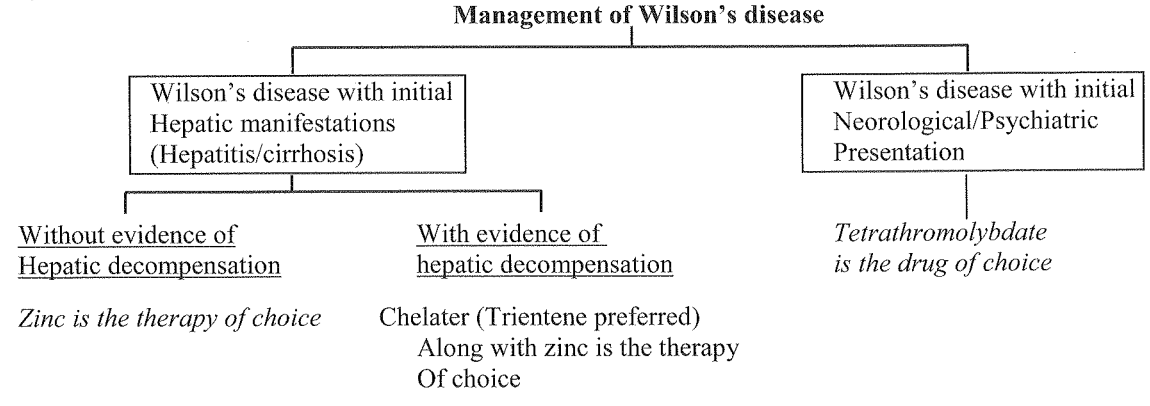
- *Present in almost all patients of Wilsons disease with Neurological /Psychiatric symptoms (99% of patients)* [Q]
- *Present in only 30-50% of patients of Wilson's disease with only hepatic manifestations*
- *Absence of KF rings does not exclude the diagnosis of Wilson's disease*[Q]
- *May* occasionally be visible to the naked eye without magnification but *definite diagnosis can only be made by an ophthalmologist using a slit lamp*[Q]

## Recommended Tests for Wilson's disease:




| Test | Wilson's Disease | Normal Value | Comment (Wilson's Disease) | Usefulness |
|---|---|---|---|---|
| *Serum Ceruloplasmin* | ***Decreased*** | 180-350mg/L (18-35 mg/dL) | Low in 90% | + |
| *KF rings* | *Present* | Absent | Present in 99% if neurologic or psychiatric symptoms present<br>Present in 30-50% in hepatic presentation/presymptomatic state | ++ |
| *24-h urine Cu* | ***Increased*** | 0.3-0.8 μmol (20-50 μg) | >1.6 μmol (>100 μg) in symptomatic patients<br>0.9 to >1.6 μmol (60 to > 100 μg) in presymptomatic patients | +++ |
| *Liver Cu* | *Increased* | 0.3–0.8 μmol/g (20-50 μg) | >3.1 μmol (>200 μg)<br>(Obstructive liver disease can cause false-positive results) | ++++ |
| *Haplotype Analysis* | *2 Matches* | 0 Matches | 2 Matches | ++++ (Siblings only) |

## Management of Wilson's disease:




***Zinc is the therapy of choice for patients with hepatitis or cirrhosis without evidence of hepatic decompensation or neuropsychiatric symptoms.Zinc is also the treatment of choice for maintainance therapy in Wilson's disease***

Zinc is the treatment of choice in Wilson's disease for

- *Initial therapy in patients with hepatitis without decompensation*[Q]
- *Maintainance therapy*
- *Presymptomatic patient*
- *Pediatric patients*
- *Pregnant patients*

# Hematochromatosis

## Hematochromatosis (Disorder of iron storage)

*Inappropriate increase in intestinal absorption results in deposition of excessive amounts of iron in parenchymal cells with eventual tissue damage and impaired function of organs*

*Serum iron ↑ed*
*% Transferrin saturation ↑ed*
*Serum ferritin ↑ed*
*Elevation in percent Transferrin saturation is the earliest phenotypic marker of herditaryhemochromatosis*[Q]

| Liver | Skin | Pancreas | Joints | Heart | *Hypogonadism* |
|---|---|---|---|---|---|
| • Usually *first organ to be affected*<br>• Hepatomegaly is seen in 95% of symptomatic patients<br>• Cirrhosis may occur (Micronodular)<br>• Hepatocellular carcinoma (30% of patients with cirrhosis).<br>• It is the *most common cause of death in treated patients.* | • ***Excessive skin (Bronzing of skin) pigmentation*** is present in 90% of symptomatic patients<br>• Usually diffuse and generalized. May be more pronounced on Face, Neck, Extensor aspect of forearm, dorsa of hands, lower legs and genitalia and ears<br>• Usually results from increased melanin and iron in dermis | Involvement of pancreas *results in Diabetes mellitus* which is seen in 65% of symptomatic patients | • ***Arthropathy*** develops in 25-50% of patients<br>• *The joints of hands especially the 2nd and 3rd MCP joints are the first to be involved*<br>• Progressive polyarthritis involving wrist, knees, hips and ankles may also be seen | • Heart is involved in 15% of symptomatic patients<br>• The most common manifestation is congestive heart failure<br>• Cardiomyopathy and cardiac arrhythmias may be seen | • Results from impairment of Hypothalmopit uitary function by iron deposition which leads to decreased production of gonadotrophins |

***The charachteristic clinical features of Haemochromatosis in order of frequency are*[Q]*:***

- *Hepatomegaly (95%)*
- *Skin pigmentation (90%)*
- *Diabetes mellitus (65%)*
- *Arthropathy (25-50%)*
- *Cardiac disease (15%)*
- *Hypogonadism*

Bronze Diabetes
*The combination of skin hyperpigmentation and insulin deficiency (diabetes) is called Bronze diabetes.*

**Tests Recommended for screening for Hereditary Hematochromatosis**

**Tests Recommended for screening for HereditaryHematochromatosis**

| Transferrin Saturation | Iron binding capacity (Unbound /Unsaturated) |
|---|---|
| • *A transferrin saturation of more than 45% is the earliest phenotypic abnormality in hereditary hematochromatosis*<br>• *Transferrin saturation is considered the best initial screening test for hereditary hematochromotosis*<br>• Transferrin saturation has a high sensitivity of >90% in diagnosing hereditary hematochromatosis | • *Unbound Iron binding capacity is an alternative screening test.*<br>• *Unbound Iron binding capacity UIBC=TIBC-Serum Iron*<br>• *Unbound iron binding capacity is decreased in hematochromatosis* |

## Treatment of Haematochromatosis

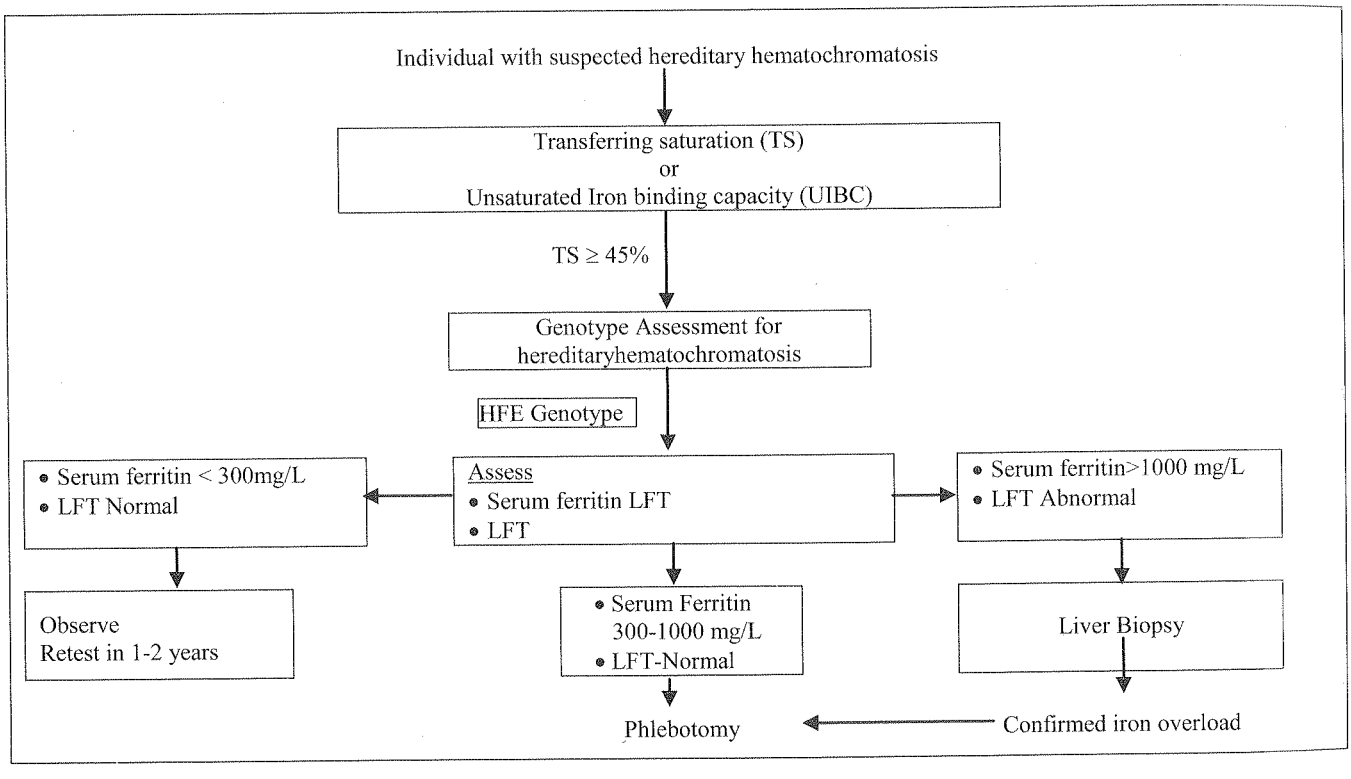
*Therapy of Haematochromatosis involves removal of excessive body iron and supportive treatment of damaged organs*

### Removal of Excessive Body iron

- ***Phlebotomy is the treatment of choice***
  Iron removal is best accomplished by once or twice weekly phlebotomy of 500ml,
  - These should be continued until the serum ferritin level is < 50μg/L (May be required for 1-2 years)
  - Thereafter phlebotomies are performed at appropriate intervals to maintain ferritin levels between 50-100μg/L (usually one phlebotomy every 3 months)
- **Chelating agents***(such as Desferoxamine) are alternative agents and indicated when anemia and hypoproteinemia are severe enough to preclude phlebotomy*

*Alcohol consumption should be eleminated*[Q] *as it increases the risk of cirrhosis in hematochromatosis nearly ten fold.*

**Algorithm for diagnosis and management of a patient with suspected Hmatochromatosis:**




**Note**

***Serum ferritin levels are a good index of body iron stores and are raised early during the cause of disease. Yet serum ferritin levels should not be used as initial screening test to detect hereditary hematochromatosis.***

***This is because serum ferritin also acts as an acute phase reactant and its levels are increased in variable infections and inflammatory conditions without iron overload. Also the serum concentration of ferritin may be increased in patients with hepatocellular injury as in viral hepatitis, alcoholic fatty liver disease or alcoholic liver diseases due to increased release from tissue cell.***

# QUESTIONS

## Jaundice

1. Following are causes of unconjugated hyperbilirubinemia, ***except***: *(AIIMS Dec 94)*
   A. Hemolytic anemia
   B. Large hematoma
   C. Rotor syndrome
   D. Megaloblastic anemia
2. Conjugated hyperbilirubinemia is seen in:
   A. Gilbert's syndrome *(AIIMS May' 2006)*
   B. Criggler Najjar syndrome
   C. Breast milk jaundice
   D. Dubin Johnson syndrome
3. Bilirubin is absent in urine because it is-
   A. Distributed in the body fat *(AIIMS Nov 99)*
   B. Conjugated with glucoron
   C. Not filtered
   D. Lipophilic
4. A young male presents with elevated bilirubin levels. Examination of urine shows presence of bilirubin while urobilonogen is absent. Likely diagnosis is:
   A. Hepatitis *(AI 1991)*
   B. Hemolytic jaundice
   C. Obstructive jaundice
   D. Gilbert's syndrome
5. A patient presents with unconjugated hyperbilirubinemia and presence of urobilinogen in urine. Which amongst the following is the least likely diagnosis: *(AI 2010)*
   A. Hemolytic jaundice
   B. Crigler Najjar syndrome
   C. Gilbert's syndrome
   D. Dubin Johnson syndrome
6. A patient presents with unconjugated hyperbilirubinemia and elevated urobilinogen levels in urine. The most likely diagnosis is: *(AI 2010)*
   A. Hemolytic Jaundice
   B. Crigler Najjar syndrome
   C. Gilbert's syndrome
   D. Dubin Johnson syndrome
7. A 8 year old child presents with Total bilirubin levels of 2.4 mg/dl Urinary Urobilinogen levels are increased and Bilirubin is absent in urine. The most likely diagnosis is *(NBE)*
   A. Hepatitis
   B. Hemolytic jaundice
   C. Obstructive jaundice
   D. Dubin Johnson's syndrome
8. A young male with gallbladder stones shows the following test results; serum bilirubin 2.5, Hb 6; urine test positive for urobilinogen; diagnosis is: *(AI 2001)*
   A. Hemolytic jaundice
   B. Obstructive jaundice
   C. Hepatocellular jaundice
   D. Protoporphyria
9. A 30 year-old male has jaundice. Blood examination shows total serum bilirubin 28 mg%, direct bilirubin 16 mg % and alkaline phosphatase 184 KA units. The Diagnosis is : *(AIIMS June 99)*
   A. Haemolytic jaundice
   B. Viral hepatitis
   C. Chronic active hepatitis
   D. Obstructive jaundice
10. A young pt presents with jaundice. Total bilirubin is 21, direct is 9.6, alkphosis 84 KA units. Diagnosis is:
    A. Hemolytic jaundice *(AI 2001)*
    B. Viral hepatitis
    C. Chronic active hepatitis
    D. Obstructive jaundice
11. True statement about unconjugated hyperbilirubinemia (select three options)
    A. 85% of the total should be indirect
    B. Seen in hemolytic anemia *(PGI Dec 05)*
    C. Seen in ↑ hemoglobin destruction (↑ bilirubin production)
    D. 50% of the total should be indirect
    E. It is seen in Biliary atresia and neonatal hepatitis
12. 5'-Nucleotidase activity is increased in: *(AI 2005)*
    A. Bone diseases.
    B. Prostate cancer.
    C. Chronic renal failure.
    D. Cholestatic disorder
13. Abnormal excretory function of hepatocytes may be assessed by: *(PGI June 07)*
    A. Increased PT
    B. Increased ALT
    C. Increased Alkaline Phosphatase
    D. Increased gamma GT
14. Increased $B_{12}$ level is seen in all, ***except***: *(AI 2000)*
    A. Cirrhosis
    B. Primary hepatocellular Ca
    C. Hepatitis
    D. Cholestatic jaundice
15. A 56 year old man presents to his internist with jaundice. The patient is receiving no medication and his only symptomatic complaints is mild fatigue over the past 2 months. Physical examination is remarkable only for the presence of scleral icterus. The patient has no significant past medical history. Analysis of serum chemistry reveals the following: *(AIIMS Nov 99)*
    SGOT : 0.58 microkat/L (35U/L)
    SGPT : 0.58 microkat/L (35U/L)
    Total bilirubin : 91.7 micron mol/L (7 mg/dL)
    Direct Bilirubin : 85.5 micron mol/L (5mg/dL)
    Alkaline phosphatase:12 micron kat/L (720U/L)
    Which of the following is the next appropriate diagnostic step?
    A. Ultrasound

B. Liver biopsy
C. Review of peripheral blood smear
D. Endoscopicretrograde cholangiopancreatography (ERCP)

16. The test used to diagnose Dubin Johnson syndrome is
A. Serum transminases *(AI 2007)*
B. BSP test
C. Hippurate test
D. Gamma glutamyl transferase level

17. True about Crigler Najjar type II syndrome is:
A. Diglucuronide deficiency *(PGI Dec 97)*
B. Recessive trait
C. Kernicterus is seen
D. Phenobarbitone is not useful

## Viral Hepatitis

### General

18. Hepatitis B virus is a *(NBE)*
A Double stranded DNA virus
B. Double stranded RNA virus
C. Single stranded DNA virus
D. Single stranded RNA virus.

19. Most common subtype of hepatitis B in India:
A. Adr *(NBE)*
B. Adw
C. Ayr
D. Ayw

20. Most common genotype of hepatitis B in India:
A. Genotype A *(NBE)*
B. Genotype B
C. Genotype C
D. Genotype D

21. Hepatitis C virus is a: *(NBE)*
A. Double stranded Enveloped DNA virus
B. Double stranded Non Enveloped RNA virus
C. Single stranded Non Enveloped RNA virus
D. Single stranded Enveloped RNA virus.

22. Hepatitis D virus is: *(NBE)*
A Double stranded DNA virus
B. Double stranded RNA virus
C. Single stranded DNA virus
D. Single stranded RNA virus.

23. A 50 year old lady presented with history of pain upper abdomen, nausea, and decreased appetite for 5 days. She had undergone cholecystectomy 2 years back. Her bilirubin was 10 mg/dl, SGPT 900 IU/L SGOT 700 IU/L and serum alkaline phosphatase was 280 IU/L. What is the most likely diagnosis -
A. Acute pancreatitis *(AIIMS Nov 05)*
B. Acute cholangitis
C. Acute viral hepatitis
D. Posterior penetration of peptic ulcer

24. Councilman Bodies are seen in: *(AIIMS Nov 07)*
A. Wilson disease
B. Alcoholic hepatitis
C. Acute viral hepatitis
D. Auto immune hepatitis

25. The commonest hepatotropic virus progressing to chronicityis : *(AIIMS May 01)*
A. HEV
B. HAV
C. HBV
D. HCV

26. Chronic hepatitis is caused by (select two options):
A. Hepatitis A *(PGI June 03)*
B. Hepatitis B
C. Hepatitis C
D. Hepatitis E
E. Hepatitis G

27. Which of the following hepatitis viruses have significant perinatal transmission : *(AI 2003)*
A. Hepatitis E virus
B. Hepatitis C virus
C. Hepatitis B virus
D. Hepatitis A virus

28. Non-parenteral hepatitis is : *(AI 2000)*
A. Hepatitis E
B. Hep B
C. Hep C
D. Hep D

29. All of the following are correctly matched, Except *(AIIMS Nov 2010)*
A. LKM1 - Autoimmune Hepatitis
B. LKM2 - Drug Induced Hepatitis
C. LKM1 - Chronic Hepatitis C
D. LKM2 - Chronic Hepatitis D

30. Which of the following viral infections is associated with highest risk of progression to fulminant disease and acute liver failure: *(NBE)*
A. HEV infection
B. HBV Infection
C. HBV/HDV coinfection
D. HDV /HBV Superinfection

31. Which of the following Hepatitis has worst prognosis *(NBE)*
A. HBV Infection
B. HDV Infection
C. HBV – HDV Coinfection
D. HDV super- infection on HBV

### Hepatitis B

32. Acute infection of hepatitis B virus is diagnosed by:
A. IgM antibody of $Hb_s$ Ag *(AIIMS Feb 97)*
B. IgM antibody of $Hb_c$ Ag
C. IgM antibody of $Hb_e$ Ag
D. IgG antibody of $Hb_c$ Ag

33. Chronic Active Hepatitis can be best differentiated from Chronic Persistant Hepatitis by: *(NBE)*
A. HBs Ag

B. Antibody to HBs Ag
C. Histopathology
D. None of the above

34. Hepatitis B can be transmitted through all of the following, except *(NBE)*
A. Semen
B. Blood
C. Breast milk
D. Fecal-oral (stool)

35. Chances of vertical transmission of Hepatitis B may be high as *(NBE)*
A. 25%
B. 40%
C. 60%
D. 90%

36. The first virological marker following acute infection with HBV is : *(AI 1999)*
A. HBs Ag
B. Anti HBs Ag
C. IgM anti HBc Ag
D. Anti HBe Ag

37. Early diagnosis of acute hepatitis-B infection is made by
A. Presence of Hbe Ag in serum *(AIIMS Nov 03)*
B. Presence of IgM anti-HBc in serum
C. Presence of Hbs Ag in serum
D. Presence of IgG anti-HBc in serum

38. Early diagnosis of active hepatitis B infection is done by : *(AIIMS June 2000)*
A. IgM HBcAg antibody
B. HBsAg
C. HBcAg
D. IgE HBsAg antibody

39. Which of the following markers in the blood is the most reliable indicator of recent hepatitis B-infection? *(AIIMS May 03)*
A. HBsAg
B. IgG anti – HBs
C. IgM anti – HBc
D. IgM anti – Hbe

40. Which of the following is a marker for Active Hepatitis B *(NBE)*
A. HBe Ag
B. IgM Anti HBs Ag
C. HBs Ag
D. Ig G Anti HB1 Ag

41. Which of the following is TRUE with regards to detectioin of HBeA g in serum: *(NBE)*
A. Signals recovery from HBV infection
B. Indicates viral repllcation and infectivity
C. An evidence for successful vaccination against Hepatitis B
D. Enhances the severity of HBV and increases the risk of cirrhosis

42. All of the following are markers of active replicative of chronic hepatitis B, except: *(AIIMS Nov 08)*
A. HBV DNA
B. HBV DNA Polymerase
C. HBeAg
D. AST & ALT

43. Which of the following is the most sensitive marker of active Hepatitis B virus replication : *(PGI 08)*
A. HBV DNA
B. HBV DNA polymerase
C. HBeAg
D. Transaminases

44. Acute hepatitis B is diagnosed by: *(PGI Dec 04)*
A. HBsAg
B. Hbe AG
C. Anti- HBs AG
D. IgM anti – HBc
E. HBV DNA

45. A 35-year-old male patient presented with history of jaundice for 15 days. The onset was preceded by a prodromal illness. His serum tested positive for HBsAg. A clinical diagnosis of acute Hepatitis B was made. What should be the next best confirmatory investigation *(AIIMS May 04)*
A. Anti-HBeAg antibody
B. HBe antigen
C. Anti-HBe IgM antibody
D. HBV DNA by PCR

46. A 29-year-old patient with jaundice is positive for HBsAg, HBeAg, and IgM anti-HBC but negative for anti-HBs and anti-HBe. The probable diagnosis is:
A. Acute Hepatitis B *(NBE)*
B. Past infection with HBV.
C. Asymptomatic carrier state.
D. Immunization with HBV vaccine

47. A thirty-year man presented with nausea, fever and jaundice of 5 days duration. The biochemical tests revealed a bilirubin of 6.7 mg/dl (conjugated 5.0 mg/dl) with SGOT/ SGPT (AST/ALT) of 1230/900 IU/ml. The serological tests showed presence of HBs Ag. IgM anti-HBc and Hbe Ag. The most likely diagnosis is: *(AIIMS Nov 02)*
A. Chronic hepatitis B infection with high infectivity.
B. Acute hepatitis B infection with high infectivity.
C. Chronic hepatitis infection with low infectivity.
D. Acute hepatitis B infection with low infectivity.

48. A male patient is observed to be HBs Ag antigen positive HBe Ag antigen negative and anti-HBe antibody positive. HBV DNA copies are observed to be 100,000/ml while SGOT and SGPT are elevated to 6 times the upper limit of normal value. What is the likely diagnosis: *(AI 2010)*
A. HBV surface mutant
B. HBV precore mutant
C. Wild HBs Ag
D. Inactive HBV carrier

49. A patient is found to be positive for HBs Ag on routine laboratory evaluation. Other serological tests for hepatitis are unremarkable. He is clinically asymptomatic and liver enzymes are within the normal range. Which of the following best describes his diagnosis: *(AI 2010)*
    A. Inactive HBV carrier
    B. Acute Hepatitis B
    C. Chronic Hepatitis B
    D. Active HBV carrier
50. The following is a marker of acute hepatitis B infection: *(AIIMS Nov 07)*
    A. DNA polymerase
    B. Hepatitis core antigen
    C. Anti HBs
    D. IgG to core antigen
51. All of the following are seen in active chronic hepatitis B except: *(AIIMS Nov 07)*
    A. IgM against core antigen
    B. Total core antibody
    C. HbeAg
    D. HbsAg
52. In a patient only Anti HBsAg is positive in serum, all other viral markers are negative. This indicates :
    A. Acute hepatitis *(AIIMS June 2000)*
    B. Chronic active hepatitis
    C. Persistent carrier
    D. Immunized person with hepatitis B vaccine
53. A patient is found to be positive only for Anti HBsAg. All other viral markers are negative.The likely diagnosis is : *(PGI 2009)*
    A. Vaccination
    B. Chronic hepatitis B
    C. Acute hepatitis B
    D. Fulminant hepatitis B
54. The marker for determining efficacy of hepatitis B vaccination is: *(NBE)*
    A. HBs Ag
    B. IgM Anti HBc
    C. IgG Anti HBc
    D. Anti – HBs Ag
55. Which of the following serum markers is indicative of HBV vaccination? *(NBE)*
    A. HBsAg
    B. Anti-HBs
    C. Anti-HBcIgM
    D. ANTI-HBc IgG
56. The only serological marker present in the 'window period' of Hepatitis B is *(NBE)*
    A. Anti HBc
    B. HBs Ag
    C. Anti HBS Ag
    D. HBe Ag
57. All of the following should be included during preliminary evaluation of a case of suspected Acute viral hepatitis except: *(AIIMS June 2000)*
    A. Hbs Ag
    B. IgM anti HBc
    C. Anti-HCV
    D. IgM anti HBe.
58. A 30-year-old patient presented with history of jaundice for 30 days. His liver function tests showed bilirubin of 100mg/dl, SGOT/SGPT-1100/1450, serum alkaline phosphatase-240 IU. He was positive for Hbs Ag. What should be the confirmatory test to establish Acute hepatitis B infection?
    A. IgM Anti-HBc antibody *(AIIMS May 06)*
    B. HbeAg
    C. HBV DNA by PCR
    D. Anti-HBc antibody
59. Hepatitis B infectivity is indicated by: *(AI 1994)*
    A. Anti-HBsAg
    B. HBsAg + HBeAg
    C. Anti-HBsAg – Anti-HBc
    D. Anti-HBeAg + Anti-Hbs Ag
60. HBV Replication is indicated by all of the following, Except: *(PGI Dec 06)*
    A. HBV DNA
    B. DNA polymerase
    C. HBe Ag
    D. HBs Ag
61. Hera lal 35 years old man was found +ve for HBsAg & HBeAg, accidentally during screening of blood donation. On Lab examination SGOT & SGPT are Normal. What should you do next : *(AI 2002)*
    A. Liver biopsy
    B. Interferon therapy
    C. Observation
    D. HBV-DNA estimation
62. A person is screened for blood Donation. Which of the following serology is safe for Blood donation.
    A. Anti HBsAg positive *(PGI June 03)*
    B. HBsAg positive
    C. Anti HBC positive (IgM)
    D. HBcAg positive
63. A blood donor is not considered for safe transfusion, if he has : *(AI 2000)*
    A. Anti HBs Ag +ve
    B. Anti HBs Ag and HBc Ag +ve
    C. Hbs Ag +ve, & IgM anti HBc +ve
    D. Anti HBe +ve
64. Reserve transcriptase of hepatitis B virus is coded on the following gene : *(AI 2000)*
    A. C gene
    B. S gene
    C. P gene
    D. X gene

65. A young male was found to be HBsAg positivity and HBe Ag negative. His liver enzymes were normal. The next step in management of this young male should be: *(AI 2008)*
   A. Lamivudine therapy
   B. Lamivudine plus IFN therapy
   C. Start IFN therapy
   D. Serial monitoring

66. A 26 year old man was observed to be positive for HBs Ag but negative for HBe Ag. The AST / ALT levls were observed to be within normal limits. The next step in management of this patient should be
   A. Serial monitoring *(NBE)*
   B. Antiviral treatment with Lamivudine monotherapy
   C. Antiviral treatment with Lamivudine and pulsed IFN
   D. Antiviral treatment with IFN Alfa alone

67. Lamivudine is recommended for treatment of chronic hepatitis B when: *(NBE)*
   A. HBe Ag positive
   B. HBe Ag Negative
   C. ALT > 2 xULN
   D. Viral DNA > 102 copies

68. Which one of the following pairs regarding Hepatitis B is not correctly matched *(AIIMS Nov 2010)*
   A. Acute Viral Hepatitis B - Supportive care
   B. Acute Viral Hepatitis B - Antiviral therapy
   C. Chronic Viral Hepatitis B - Supportive care
   D. Chronic Viral Hepatitis B - Antiviral therapy

69. All of the following statements about Hepatitis B are true, Except *(AIIMS Nov 2010)*
   A. Vertical Transmission is more common than horizontal transmission in non-endemic areas
   B. Age of onset determines prognosis
   C. Period of communicability lasts several months
   D. Virus can be detected in blood one month before jaundice

70. Extrahepatic Manifestations of Hepatitis B include all of the following Except *(PGI June 01)*
   A. Aplastic Anemia
   B. Gullian Barre syndrome
   C. Pancreatitis
   D. Gall stone disease
   E. Cryoglobulinemia

71. HBs Ag positive person may have all of the following associated Renal lesions, Except: *(PGI Dec 06)*
   A. Membranous Glomerulonephritis (MGN)
   B. Membrano proliferative Glomerulnephritis (MPGN)
   C. Mesangiocapillary Glomerulonephritis
   D. Focal Segmental Glomerulosclerosis (FSGS)

72. Interferon treatment is recommended in chronic hepatitis B in patients with: *(PGI June 07)*
   A. ↑ HBV DNA and Normal ALT
   B. ↑ HBV DNA and ↑ ALT
   C. ↑ HBV DNA and compensated cirrhosis
   D. ↑ HBV DNA and decompensated cirrhosis

73. Agents Recommended for treatment of chronic Hepatitis B include all of the following, Except. *(PGI June 05)*
   A. Interferon
   B. Lamuvudine
   C. Adefovir
   D. Entecevir
   E. Famcyclovir

74. First Line drug of choice for hepatitis:
   A. Entecavir *(NBE)*
   B. Sofosbuvir
   C. Simeprevir
   D. Tenofovir

75. All following are at-risk group adults meriting Hepatitis B vaccination in low endemic areas except: *(NBE)*
   A. Patients on chronic hemodialysis
   B. Diabetics on insulin
   C. Medical/nursing personnel
   D. Patients with chronic liver disease

76. Best site of giving hepatitis B vaccine is:
   A. Subcutaneous *(NBE)*
   B. Intradermal
   C. Intra-muscular deltoid
   D. Intra-muscular gluteal

## Hepatitis C

77. Chronic liver disease is most commonly caused by :
   A. Hepatitis B *(AI 2000)*
   B. Hepatitis A
   C. Hepatitis C
   D. Hepatitis E

78. Hepatitis C virus is associated with : *(AI 2000)*
   A. Anti LKM antibody
   B. Scleroderma
   C. Cryoglobulinemia
   D. Polyarteritis nodosa

79. Extrahepatic Manifestations of Hepatitis C include all of the following Except: *(PGI June 04)*
   A. Lichen Planus
   B. Celiac Disease
   C. Glomerulonephritis
   D. Cryoglobulinemia
   E. Polyarthritis

80. Hepatic C is associated with all except:
   A. PAN *(PGI June 08)*
   B. Dermatomyositis like syndrome
   C. Lichen Planus
   D. Psoriasis

81. A 30 year old patient with H/O antibodies to HCV for 6 months duration and his AST/ALT is normal. There is no symptom or stigmata of liver disease. The most appropriate approach: *(PGI June 04)*
    A. Reassure the patient
    B. Repeat titre every three years
    C. Repeat enzymes every year
    D. Do liver biopsy & start antiviral drugs accordingly.
82. A 30 year old patient with H/O persistant antibodies to HCV for 6 months duration and his AST/ALT is normal. There is no symptom or stigmata of liver disease. The most appropriate approach:
    A. Reassure the patient *(PGI June 04)*
    B. Repeat titre every three years
    C. Repeat enzymes every year
    D. Do liver biopsy & start antiviral drugs accordingly.
    E. Determine HCV RNA levels
83. A 55 year old male patient was diagnosed to have chronic hepatitis C. He responded to treatment with interferon. However, after one year of follow up he showed a relapse of disease. Which of the following would be the next most appropriate choice?
    A. Ribavarin and interferon *(AIIMS Nov 03)*
    B. Lamivudine and interferon
    C. Nevirapine and lamivudine
    D. Indinavir and ribavarin.
84. A 55 year old male patient was diagnosed to have chronic hepatitis C. He responded to treatment with interferon. However, after one year of follow up he showed a relapse of disease. Which of the following would be the next most appropriate choice?
    A. Ribavarin and interferon *(AIIMS Nov 03)*
    B. Lamivudine and interferon
    C. Nevirapine and lamivudine
    D. Indinavir and ribavarin.
85. Sustained Response to antiviral therapy (IFN + Ribavarin) in hepatitis C is indicated by
    A. High HCV-RNA *(PGI Dec 04)*
    B. Cirrhosis
    C. Age > 40 years
    D. Genotype I
    E. Female sex

## Hepatitis E

86. True regarding hepatitis E virus is: *(AIIMS Dec 98)*
    A. Seen in Post transfusion cases
    B. Associated with increased mortality in pregnant female
    C. Associated with hepatitis B virus
    D. Acquired by feco-oral route
87. The most common route of spread in hepatitis E is:
    A. Blood transfusion *(AI 1995)*
    B. Feco-oral
    C. Intercourse
    D. IV injection
88. During an epidemic of hepatitis E, Fatality is maximum in : *(AI 2000)*
    A. Pregnant women
    B. Infants
    C. Malnourished male
    D. Adolescents
89. Fulminant Hepatitis E is typically seen in: *(NBE)*
    A. Pregnant women
    B. Infants
    C. Adolescents
    D. Malnourished males
90. Which hepatitis is most dangerous in pregnancy:
    A. Hepatitis A *(AIIMS May 95)*
    B. Hepatitis B
    C. Hepatitis C
    D. Hepatitis E
91. Which hepatitis virus has worst prognosis in pregnancy : *(AIIMS Feb 97)*
    A. HBV
    B. HCV
    C. HEV
    D. HAV
92. Most common type of hepatitis responsible for epidemics in India is : *(AI 1997)*
    A. Hepatitis A
    B. Hepatitis B
    C. Hepatitis C
    D. Hepatitis E
93. Most common cause of acute sporadic hepatitis in India is *(NBE)*
    A. Hepatitis E
    B. Hepatitis B
    C. Hepatitis C
    D. Hepatitis D

## Autoimmune and Granulomatous Hepatitis

94. Characteristic Auto antibodies of Autoimmune Hepatitis include all of the following, Except:
    A. Antinuclear Antibodies (ANA) *(PGI Dec 06)*
    B. Anti SLA
    C. Anti LKM1
    D. ANCA
95. Granulomatous hepatitis may be seen with :
    A. Carbamazepine *(AI 1996)*
    B. Allopurinol
    C. Phenylbutazone
    D. All of the above

## Alcoholic Hepatitis

96. Features of Alcoholic hepatitis include all of the following except: *(AI 1991)*

A. Elevated bilirubin
B. Prolonged prothrombin time
C. Elevated serum albumin
D. Anemia

97. Ratio of AST/ALT > 1 is present in *(AIIMS May 07)*
A. Non alcoholic steatohepatitis
B. Alcoholic hepatitis
C. Wilson's disease
D. All of the above

98. Which is **not** true about alcoholic hepatitis :
A. Gamma glutamyl transferase is raised
B. SGPT is raised > SGOT *(AIIMS May 95)*
C. SGOT is raised > SGPT
D. Alkaline phosphatase is raised

99. Which of the following enzyme assay is useful to diagnose alcoholism *(AIIMS Dec 94)*
A. SGOT
B. SGPT
C. Alkaline phosphatase
D. Glutamyl aminotransferase

100. Maddrey discriminant score is used for determining mortality due to: *(NBE)*
A. Alcoholic hepatitis
B. Viral hepatitis
C. Cryptogenic hepatitis
D. Hepatic encephalopathy

101. Zieve syndrome is characterized by all except: *(NBE)*
A. Alcohol abuse
B. Hemolysis
C. Hyperlipidemia
D. Pancreatic lipase deficiency

102. Which is useful to decrease mortality and renal failure in acute liver disease due to alcoholism:
A. Pentoxyfylline *(AIIMS May 07)*
B. Orlistat
C. S-Adenosyl methionine
D. Syrlamysin

## Non Alcoholic Fatty Liver Disease (NAFLD/NASH)

103. Non Alcoholic steatohepatitis is seen in all, except:
A. Diabetes *(PGI June 05)*
B. Obesity
C. Hypertriglyceridemia
D. Total Parentral Nutrition
E. Gall stone disease

104. All of the following statements about Non Alcoholic Fatty Liver disease are true, except: *(PGI June 01)*
A. Common in Diabetics
B. Clofibrate provides effective treatment
C. Commonest cause of cryptogenic cirihosis
D. Associated with elevated transminases

## Ascitis

105. Chylous ascities is caused by all of the following ***except***: *(AIIMS Nov 02)*
A. Colloid carcinoma of stomach.
B. Tuberculosis.
C. Trauma.
D. Nephrotic syndrome.

106. Endemic ascites is caused due to:
A. Field fungae *(NBE)*
B. Sanguinarine
C. Fusarium toxins
D. Pyrrolizidine alkaloids

107. Endemic ascites is associated with:
A. Pyrrolizidine *(NBE)*
B. Aflatoxin
C. BOAA
D. Sanguinine

108. Which of the following statement about ascitis is true: *(PGI June 05)*
A. Hemorrhagic ascitis is diagnosed when RBC count > 1,000/$mm^3$
B. SBP is diagnosed when Neutrophil count > 500/$mm^3$
C. Large volume paracentesis is indicated in SBP
D. USG can detect as little as 100 ml of peritoneal fluid
E. Norfloxacin is the drug of choice in SBP

109. First line of treatment in Ascitis is: *(PGI June 96)*
A. Salt Restriction
B. Diuretics
C. Paracentesis
D. Shunt

## Cirrhosis and its Complications

### Cirrhosis: General

110. Micronodular cirrhosis is commonly seen in all except: *(AIIMS Nov 07)*
A. Chronic hepatitis B
B. Alcoholic liver disease
C. Hemochromatosis
D. Chronic extrahepatic biliary obstruction

111. In hepatic cirrhosis, which of the following is increased: *(PGI June 97)*
A. Alpha 1 globulin
B. Alpha 2 globulin
C. Gamma globulin
D. All of the above

112. Which of the following is associated with chronic liver disease? *(NBE)*
A. Hepatitis A
B. Chronic Malaria
C. Infectious Mononucleosis
D. Alpha-1 Antitrypsin deficiency

113. A patient presents with esophageal varices and a liver span of 10cm. All of the following are likely causes, except: *(PGI Dec 04)*
A. Haemochromatosis
B. Alcoholic liver disease

C. Veno-occlusive disease
D. Post necrotic cirrhosis
E. Budd-chiary syndrome

114. Enlarged liver with Hepatocellular dysfunction may be seen in all of the following, except:
A. Wilson's disease *(PGI June 05)*
B. Budd Chirai syndrome
C. Alcoholic hepatitis
D. NASH
E. Post necrotic syndrome

## Primary Biliary Cirrhosis & Sclerosing Cholangitis

115. Most common symptom of primary biliary cirrhosis is
A. Pruritis *(AI 1996)*
B. Abdominal pain
C. Jaundice
D. Bleeding

116. Antibodies usually elevated in primary biliary cirrhosis are: *(AI)*
A. Antiactin antibodies
B. Antinuclear antibodies
C. Antimitochondrial antibodies
D. Antisoluble liver antigen antibodies

117. All of the following statements about primary sclerosing cholangitis are true, Except: *(AI 1992)*
A. Increased risk associated with smoking
B. Associated with Ulcerative colitis
C. GGT elevation occurs early
D. Pruiritis is a common presenting symptom

118. All of the following statements about primary sclerosing cholangitis are true, Except: *(PGI Dec 03)*
A. Increased incidence in females
B. Associated with Inflammatory bowel disease
C. May involve both intra and extra hepatic ducts
D. ERCP is a sensitive investigation

119. All of the following statements are correct. Except:
A. Antimitochondrial antibodies are positive in primary biliary cirrhosis *(NBE)*
B. In late stage of PSC treatment is liver transplantation
C. In advanced stages of cirrhosis major blood supply to liver comes from Hepatic vein
D. Elevated lipoprotein-X in PBC

## Non Cirrhotic Portal Fibrosis

120. A child presents with massive hemetemesis and systemic hypotension. He has no fever or other significant history. Examination reveal massive splenomegaly but no hepatomegaly. Likely diagnosis is *(AIIMS Nov 01)*
A. Hepatocellular carcinoma
B. Bleeding duodenal ulcer
C. Oesophageal varices
D. Non-cirrhotic portal fibrosis

121. A 12 year old boy presents with hemetemesis, malena and mild splenomegaly. There is no obvious jaundice or ascitis. The most likely diagnosis is:
A. EHPVO
B. NCPF
C. Cirrhosis
D. Malaria with DIC

122. A 23 year old male has presented with repeated episodes of hematemesis. There is no history of jaudice or liver decompensation. On examination ther significant findings include splenomegaly (8 cms below costal margin), and presence of esophageal varices. There is no ascites or peptic ulceration. The liver function tests are normal. The most likely diagnosis is : *(AI)*
A. Extahepatic portal venous obstruction
B. Non cirrhotic portal fibrosis
C. Cirrhosis
D. Hepatic venous outflow tract obstruction

123. Ingestion of arsenic causes : *(AIIMS May 01)*
A. Hepatic carcinoma
B. Hepatic adenoma
C. Non cirrhotic portal fibrosis
D. Hepatic cirrhosis

124. Which of the following is the most common presenting symptom of non-cirrhotic portal hypertension? *(AI 2006)*
A. Chronic liver failure
B. Ascites
C. Upper gastrointestinal bleeding
D. Encephalopathy

## Portal Hypertension

125. In patients with cirrhosis of the liver the site of obstruction in the portal system is in the : *(AI 2004)*
A. Hepatic vein
B. Post sinusoidal
C. Extra hepatic portal vein
D. Sinusoids

126. Normal portal venous pressure is: *(AI 1994)*
A. 3-5 cm saline
B. 5-10 cm saline
C. 10-15 cm saline
D. 15-20 cm saline

127. An 18 yr old male presents with massive hematemesis; he has history of fever for the past 14 days for which he was managed with drugs; moderate splenomegaly is present; diagnosis is: *(AI 2001)*
A. NSAID induced duodenal ulcer
B. Drug induced gastritis
C. Esophageal varices
D. None of the above.

128. A young boy, Rahul presents with massive hemetemesis. He had fever for 15 days few days back

which was treated with few drugs. Clinical examination reveal moderate splenomegaly). No other history is positive) Probable diagnosis is:
A. Drug induced gastritis *(AIIMS Nov 01)*
B. Oesophageal tear
C. Bleeding duodenal ulcer
D. Oesophageal varices

129. A young patient presenting with massive hematemesis was found to have splenomegaly. In this case the most likely source of bleeding is:
A. Duodenal ulcer
B. Esophageal varices
C. Erosive mucosal disease
D. Gastric ulcer

130. A man presents with history of hemetemesis of about 500 ml of blood. On examination, spleen is palpable 5 cms below the left costal margin. The most likely diagnosis is: *(AI 2012)*
A. Portal Hypertension
B. Gastric ulcer
C. Drug induced
D. Mallory Weiss Tear

131. All can be used as endoscopic sclerosants in the treatment of variceal bleeding, ***except***:
A. Polydochyl *(AIIMS Nov 01)*
B. Cynoacrylate
C. Alcohol
D. Acetic acid

132. A 40 year old patient, a known case of cirrhosis develops acute episode of GI bleed. Initial therapy given for 6 hours. Which of the following procedure is useful : *(AIIMS June 99)*
A. Nasogastric aspiration
B. Urgent endoscopy
C. Sedation
D. Ultrasound

133. For the treatment of which of the following is the Sengstaken-Blakemore tube used:
A. Epistaxis
B. Urethral injury
C. Urinary retention
D. Bleeding from esophageal varices

134. *Sengstaken - Blakemore tubes:*
A. Have three lumens - gastric balloon, esophageal balloon and esophageal aspiration port
B. Control around 90% of cases of variceal bleeding
C. When correctly sited, should be attached to 5 kg of traction
D. Usually have the esophageal balloon inflated before the gastric balloon

135. Rockall score is used for prognosis of patients of:
A. Upper GI bleeding
B. Lower GI bleeding
C. Hepatic encephalopathy
D. IBD

136. Forrest classification is used for evaluating:
A. Upper GI bleeding
B. Liver transplantation
C. Lower GI bleeding
D. Familial adenomatous polyposis

137. A 45 - year old cirrhotic patient presented with severe haematemesis. The management of choice is :
A. Whole blood transfusion is the best
B. Colloids are preferred over crystalloids
C. Normal saline infusion *(AIIMS June 99)*
D. IV fluid with diuretics

## Hepatic Encephalopathy / Hepatic failure

138. The most common cause of Acute liver failure in India is:
A. Hepatitis A
B. Hepatitis B
C. Hepatitis C
D. Hepatitis I

139. The most common viral cause of Acute liver failure worldwide is:
A. Hepatitis A
B. Hepatitis B
C. Hepatitis C
D. Hepatitis E

140. Hepatic-encephalopathy may be precipitated by all of the following ***except*** : *(AI 1999)*
A. Anemia
B. Barbiturates
C. Hyperkalemia
D. Hypothyroidism

141. Stigmata of chronic Liver disease include all of the following, except
A. Parmar Erythema
B. Spinder naevi
C. Testicular Atrophy
D. Subcutaneous nodules

142. All of the following are signs of chronic liver failure, Except:
A. Palmer erythema
B. Spider nevi
C. Testicular atrophy
D. Subcutaneous nodules

143. Skin stigmata of Liver disease include all of the following, Except
A. Parmar Erythema
B. Paper money skin
C. Drumstick fingers
D. Subcutaneous nodules

144. Which of the following is *not* a precipitating factor for hepatic encephalopathy in patients with chronic liver disease? *(AIIMS May 05)*
A. Hypokalemia

B. Hyponatremia
C. Hypoxia
D. Metabolic acidosis

145. Hepatic Encephalopathy is predisposed by all, Except: *(PGI June 03)*
A. Hyperkalemia
B. Dehydration
C. Constipation
D. G1 Bleeding
E. SBP

146. Features of Acute Fulminant Hepatic failure include all of the following Except: *(PGI June 01)*
A. Hyperglycemia
B. Hypomagnesemia
C. Hepatorenal syndrome
D. Intracranial hemorrhage
E. Coagulopathy

147. In child with acute liver failure, the most important prognostic factor for death is- *(AIIMS 06)*
A. Increasing transaminase
B. Increasing bilirubin
C. Increasing prothrombin time
D. Gram negative sepsis

148. In patients with acute liver failure, the best prognostic indicator is: *(AIIMS May 01)*
A. Serum albumin
B. Serum alpha feto protein
C. Serum bilirubin
D. Factor V estimation

149. The first laboratory test that becomes abnormal in acute hepatocellular failure is: *(NBE)*
A. Prothrombin time (PT)
B. APTT
C. Decreased Albumin
D. Increased Arterial Ammonia

150. A symmetric high-voltage, triphasic slow wave pattern is seen on EEG in the following
A. Hepatic encephalopathy *(AIIMS May 06)*
B. Uremic encephalopathy
C. Hypoxic encephalopathy
D. Hypercarbic encephalopathy

151. Flapping Tremors may be associated with all of the following, Except *(NBE)*
A. Hepatic encephalopathy
B. Uremia
C. $CO_2$ Narcosis
D. Thyrotoxicosis

152. Alzheimer type II astrocyte are not seen in:
A. Hepatic encephalopathy *(NBE)*
B. Alzheimer's disease
C. Wilson's Disease
D. Urea Cycle Disorders

153. Following liver transplantation, recurrence of primary disease in the liver most likely occures in:
A. Wilson disease *(AIIMS Nov. 05)*
B. Autoimmune hepatitis
C. Alpha - 1 antitrypsin deficiency
D. Primary biliary cirrhosis

## Hepatorenal Syndrome

154. Features of Hepatorenal syndrome are (select two options): *(PGI June 06)*
A. Urine sodium < 10 meq/l
B. Normal renal histology
C. Renal function abnormal even after liver become normal
D. Proteinuria < 500 mg/day

155. Which of the following statements is incorrect with regard to Hepatorenal syndrome in a patient with cirrhosis
A. Createnine clearance < 40 ml/min *(AI 2003)*
B. Urinary sodium < 10mq/L
C. Urine osmolality lower than plasma osmolality
D. No sustained improvement in renal function after volume expansion.

156. Which of the following statements is incorrect with regard to heptorenal syndrome in a patient with cirrhosis
A. The creatinine clearance is > 40 ml/min
B. The urinary sodium is less than 10 mmol/L
C. The urine osmolality is lower than the plasma osmolality *(AIIMS Nov 2004)*
D. There is poor response to volume expansion

## Hepatocellular Carcinoma

157. All of the following are risk factors for Hepatocellular carcinoma ***except***: *(All India)*
A. Hepatitis C infection
B. Alcoholism
C. Alfatoxins
D. Animal fat in diet

158. Lalloo, 60 years of age, a known case of cirrhosis liver, presents with increased levels of Alpha feto protein, hepatomegaly 3 cm below costal margin.USG showed lesions involving the right lobe of the liver. What is the most probable diagnosis :
A. Focal nodular hyper-plasia *(All India)*
B. Hepatocellular carinoma
C. Hepatic adenoma
D. Metastasis

159. All of the following are important clinical manifestations of hepatocellular carcinoma ***except***:
A. Jaundice *(All India)*
B. Abdominal pain
C. Abdominal mass
D. Ascitis

160. 38 year old man Babbu, a chronic alcoholic, presents with pain in abdomen. On examination his liver is enlarged and serum α fetoprotein is elevated. The most likely diagnosis is: *(AI 2000)*
A. Hepatocellular carcinoma
B. Liver cell hyperplasia

C. Hepatic adenoma
D. Hepatitis

161. Increase in alpha-fetoprotein is seen in : *(AIIMS June 2000)*
A. Hepatoblastoma
B. Neuroblastoma
C. Thymoma
D. Angiosarcoma

162. Which of the following statements is not true regarding α-fetoprotein : *(AI 1999)*
A. High levels are seen in fibrolamellar hepatic carcinoma
B. Pre-operative high level indicates worse prognosis
C. High level are seen in stomach carcinoma
D. Levels may be increased in hepatitis

163. All are features of hepatocellular carcinoma, ***except***: *(AIIMS Sept 96)*
A. Not common in Asian
B. Liver biopsy is diagnostic
C. Raised titre of HBV and HCV antibodies
D. Fibrolameller type is having good prognosis

164. About fibrolamellar carcinoma, TRUE is : *(AIIMS May 94)*
A. Diffuse in nature
B. Occurs after 60 years of age
C. Cirrhosis is the most common presenting feature
D. Has better prognosis

165. All of the following are true about fibrolamellar carcinoma of the liver ***except*** : *(AI 2001)*
A. More common in females
B. Better prognosis than HCC
C. AFP levels always greater than 1000
D. Occur in younger individuals

## Budd Chiari Syndrome

166. Budd-chiari syndrome is most commonly due to: *(AI 1999)*
A. Hepatic vein obstruction
B. Acute portal hypertension
C. Congenital portal hypertension
D. IVC- obstruction

167. What is the most common cause for Budd chiari syndrome : *(AIIMS Nov 2000)*
A. Right ventricular failure
B. PNH
C. Valve in hepatic veins
D. Polycythemia vera

168. Commonest cause of Budd Chiary syndrome is: *(AI 1997)*
A. Valve in the IVC
B. Hepatocellular carcinoma
C. Paroxysmal nocturnal hemoglobinuria
D. Renal cell carcinoma

169. Most common cause of Budd Chiari syndrome is: *(AIIMS May 97)*
A. Idiopathic
B. Valves in hepatic veins
C. Hepatocellular carcinoma
D. Thrombosis of hepatic veins

170. In Budd Chiari syndrome, the site of venous thrombosis is : *(AI 2004)*
A. Infrahepatic inferior vena cava
B. Infrarenal inferior vena cava
C. Hepatic veins
D. Portal veins

171. The following is the least likely manifestation of Acute Budd-Chiari syndrome: *(NBE)*
A. Enlarged tender liver
B. Ascites
C. Jaundice
D. Venous collaterals

## Disorders of Biliary Tract

172. 5'-Nucleotidase activity is increased in: *(AI 2005)*
A. Bone diseases
B. Prostate cancer.
C. Chronic renal failure.
D. Cholestatic disorders.

173. Lithogenic bile has the following properties :
A. ↓ Bile and ↑ Cholesterol ratio *(AI 1996)*
B. ↑ Bile and ↓ cholesterol ratio
C. Equal bile and cholesterol
D. Cholesterol only

174. Gall bladder stone formation in influenced by all ***except:*** *(AI 1998)*
A. Clofibrate therapy
B. Hyperalimentation
C. Primary biliary cirrhosis
D. Hypercholesterolemia

175. Stone formation in Gall bladder is enhanced by all ***except*** : *(AI 1996)*
A. Clofibrate therapy
B. Ilial resection
C. Cholestyramine therapy
D. Vagal stimulation

176. Incidence of gall stone is high in: *(AIIMS Nov 93)*
A. Partial hepatectomy
B. Ileal resection
C. Jejunal resection
D. Subtotal gastrectomy

177. True statement about gall stones are All/Except:
A. Lithogenic bile is required for stone formation
B. May be associated with carcinoma gall bladder
C. Associated with diabetes mellitus *(AIIMS Nov 99)*
D. More common in males between 30-40 years of age

178. Most common site for impaction of gell stones in gall stone lieus is : *(AI 1999)*
A. Ist part of duodenum
B. IInd part of duodenum
C. Terminal ileum
D. Colon

179. The most common site of intestinal obstruction in gallstone ileus is: *(AIIMS May 05, AI 04)*
   A. Duodenum
   B. Jejunum
   C. Ileum
   D. Sigmoid colon

180. Internal fistula is most common between gall bladder and: *(AIIMS June 93)*
   A. Colon
   B. Duodenum Ist part
   C. Jejunum
   D. Transverse colon

181. The treatment of choice for silent stones in Gall bladder is : *(AI 1997)*
   A. Observation
   B. Chenodeoxycholic acid
   C. Cholecystectomy
   D. Lithotripsy

182. Which of the following is not an indication for cholecystectomy: *(AIIMS May 05)*
   A. A. 70 year old male with symptomatic gall stone
   B. B. 20 years old male with sickle cell anemia and symptomatic gallstones
   C. C. 65 year old female with a large gallbladder polyp
   D. D. 55 year old with an asymptomatic gallstone

183. A 69 year old male patient having coronary artery disease was found to have gall bladder stones while undergoing a routine ultrasound of the abdomen. There was no history of biliary colic or jaundice at any time. What is the best treatment advice for such a patient for his gallbladder stones:
   A. Open cholecystectomy *(AIIMS Nov 03, AI 03)*
   B. Laparoscopic cholecystectomy
   C. No surgery for gallbladder stones
   D. ERCP and removal of gallbladder stones

184. Medical treatment for gall bladder stone is amenable for : *(AI 1998)*
   A. Stones less than 15 mm in size
   B. Radioopaque stone
   C. Calcium bilirubinate oxalate stone
   D. Nonfunctioning stones associated with gall bladder

185. All of the following are required for visualization of gall bladder in an oral cholecystogram ***except***:
   A. Motor mechanism of gall bladder *(AI 1997)*
   B. Patency of cystic duct
   C. Ability to absorb water
   D. Functioning hepatocytes

186. All are component of saint's triad except:
   A. Renal stones *(AIIMS Nov 95)*
   B. Hiatus hernia
   C. Diverticulosis coli
   D. Gall stones

187. Charcot's triad includes all of the following ***except***
   A. Pain *(AI 1996)*
   B. Fever
   C. Jaundice
   D. Vomiting

188. Incorrect about Mirrizi syndrome:
   A. Jaundice *(NBE)*
   B. Cystic duct obstruction
   C. Cholecystocholedochal fistula
   D. Hemobilia

189. Tokyo Guidelines are used for diagnosis and severity assessment of: *(NBE)*
   A. Acute Appendicitis
   B. Acute Cholecystitis
   C. Acute Pancreatitis
   D. Irritiable Bowel Syndrome

190. All of the following are known predesposing factors for cholangiocarcinoma ***except*** :
   A. CBD stones *(AI 1997)*
   B. Clonorchis sinensis
   C. Ulcerative colitis
   D. Primary sclerosing cholangitis

191. Which of the following does not predispose to Cholangiocarcinoma *(AI 1996)*
   A. Ulcerative colitis
   B. Clonorchis sinensis
   C. Choledochal cyst
   D. Chronic pancreatitis

192. Risk factors for malignant change in an asymptomatic patient with a gall bladder polyp on ultrasound include all of the following, Except: *(AI 2009)*
   A. Age > 60 years
   B. Rapid increase in size of polyp
   C. Size of polyp > 5 mm
   D. Associated Gall stones

## Wilson's Disease

193. All the following are features of Wilson's disease ***except***: *(AI 1996)*
   A. Increased copper content in liver
   B. Increased ceruloplasmin
   C. Mental changes
   D. Features of chronic active hepatitis

194. Wilson's diseases, features are all except: *(NBE)*
   A. Sunflower Cataract
   B. Tremors
   C. Pronounced sensory changes
   D. Renal Calculi may be seen

195. All of the following statements about Wilson's disease are true, Except: *(NBE)*
   A. Autosomal dominant Inheritance
   B. Hemolytic anemia
   C. Low serum ceruloplasmin
   D. Mutation on Chromosome 13

196. Which of the following statements about Wilson's disease is true: *(AI 2010)*
   A. Low serum ceruloplasmin and low urinary copper
   B. Low serum ceruloplasmin and high urinary copper
   C. High serum ceruloplasmin and low urinary copper
   D. High serum ceruloplasmin and high urinary copper

197. A 12 years old girl with tremors and emotional liability has golden brown discolouration in liability has golden brown discolouration in liability has golden brown discolouration in Descement's membrane. The most likely diagnosis is-
   A. Fabry's disease *(AI 04)*
   B. Wilson's disease
   C. Glycogen storage disease
   D. Acute Rheumatic fever

198. All of the following are features of wilson's disease, except- *(AIIMS Dec 97)*
   A. Hemolytic anemia
   B. Testicular atrophy
   C. Chorea
   D. Chronic active hepatitis

199. Kayser- Fleischer rings (KF rings) are seen in:
   A. Pterygium *(AI 2010)*
   B. Hematochromatosis
   C. Wilson's disease
   D. Menke's kinked hair syndrome

200. All of the following statements about. Wilson's disease are true, EXCEPT- *(AIIMS May 04)*
   A. It is an autosomal recessive disorder
   B. Serum ceruloplasmin level is < 20 mg/dl
   C. Urinary copper excretion is <100 μg/dl
   D. Zinc acetate is effective as maintenance therapy

201. A 14 year old boy presents wit recurrent episodes of hepatitis Opthalmoscopic evalution reveals KF rings and serum ceruloplasmin levels are < 20 mg/dl. The treatment of choice for initial therapy is *(NBE)*
   A. Zinc
   B. Pencillamine
   C. Tetrathromolybdate
   D. Hepatic transplantation

202. Low serum copper due to ATP 7A gene is due to?
   A. Dubin-Johnson's syndrome
   B. Wilson disease *(NBE)*
   C. Menke disease
   D. Gilbert's disease

## Hemochromatosis

203. A patient presents with Arthritis, hyperpigmentation of skin andhypogonadism, likely diagnosis is-
   A. Hemochromatosis *(AI 2001)*
   B. Ectopic ACTH secreting tumour of the lung
   C. Wilson's disease
   D. Rheumatoid arthritis

204. Which of the following is least commonly involved organ system in Hemochromatosis: *(NBE)*
   A. Liver
   B. Skin
   C. Joints
   D. Eye

205. A patient presents with fasting blood sugar of 167mg/dl, skin pigmentation and hypogonadism. His liver enzymes show SGOT as 670 and SGPT AS 690. Which of the following is the most likely diagnosis? *(NBE)*
   A. Alpha-1 Antitrypsin Deficiency
   B. Wilson's Disease
   C. Hemochromatosis
   D. Glycogen Storage Disease

206. Earliest phenotypic manifestation of Idiopathic hereditary hemochromatosis is- *(AIIMS May 07)*
   A. Post prandial increase in serum iron concentration
   B. Elevated serum ferritin level
   C. Slate grey pigmentation of skin
   D. Increased transferrin saturation

207. The first test to become positive in patients with Hemochromatosis is: *(NBE)*
   A. Increased Serum Iron
   B. Increased Serum Ferritin
   C. Increased Transferrin Saturation
   D. Increased Liver Enzymes

208. Lallo, aged 54 years, who is a known diabetic patient develops cirrhosis. There is associated skin hyperpigmentation and restrictive cardiomyopathy which of the following is the best initial test to diagnose this case. *(AIIMS Nov 2000)*
   A. Iron binding capacity
   B. Serum ferritin
   C. Serum copper
   D. Serum ceruloplasmin

209. Investigation of choice to confirm Hemochromatosis as the cause of cardiomyopathy is: *(NBE)*
   A. ECG
   B. Echo
   C. MRI
   D. CT

210. All are seen in hemochromatosis except- *(NBE)*
   A. Hypogonadism
   B. Arthropathy
   C. Bronze diabetes
   D. Desferrioxamine is the treatment of choice.

## Miscellaneous

211. What is the uppermost intercostal space used for hepatic biopsy: *(NBE)*
   A. 5th
   B. 7th
   C. 9th
   D. 11th

212. What is the most common intercostal space used for hepatic biopsy: *(NBE)*
   A. 5th
   B. 6th
   C. 7th
   D. 8th

213. Menghini's needle is used for: *(NBE)*
   A. Pleural aspiration
   B. Lumbar puncture
   C. Kidney biospy
   D. Liver biospy

214. Which of the following statements regarding liver enzymes is true *(NBE)*
   A. ALT is less specific indicator of liver injury than AST
   B. Absolute levels of aminotransferase correlate with outcome
   C. Glutathione-S- Transferase is used as a hepatic prognostic marker after surgery
   D. None of the above

215. Increased LDH is an important marker for:
   A. Bulky Disease *(NBE)*
   B. Lymphoma
   C. Liver metastasis
   D. Lung metastasis

216. Significant weight loss is defined as: *(NBE)*
   A. 5% weight loss in 1-2 months
   B. 5% weight loss in 2-3 months
   C. 10% weight loss in 1-2 months
   D. 10% weight loss in 2-3 months

217. Milan criteria is used for: *(NBE)*
   A. Liver transplantation
   B. GERD staging
   C. Cirrhosis staging
   D. Hepatic encephalopathy staging

218. M.E.L.D score includes all except:
   A. Bilirubin *(NBE)*
   B. INR
   C. Serum creatinine
   D. Serum albumin

219. Maddrey discriminant score is used for determining mortality due to: *(NBE)*
   A. Alcoholic hepatitis
   B. Viral hepatitis
   C. Cryptogenic hepatitis
   D. Hepatic encephalopathy

220. Indications for Liver Transplantation include:
   A. Hemochromatosis *(PGI 09)*
   B. Primary Biliary Cirrhosis
   C. Sclerosing cholangitis with ulcerative colitis
   D. Sclerosing cholangitis without ulcerative colitis
   E. Biliary

221. Quantitative assessment of liver function can be done by: *(PGI Dec 05)*
   A. Degree of ↑ Transaminases
   B. Degree of ↑ Alkaline phosphatase
   C. Degree of ↑ GGT
   D. Estimation of Galactose Elimination capacity

222. Hepatomegaly is a feature of all of the following, Except : *(AI 2009)*
   A. Von Girke's Disease
   B. Hurler's Disease
   C. Nieman Pick Disease
   D. Hepatic porphyrias

223. Which one of the following serum levels would help in distinguishing an acute liver disease from chronic liver disease? *(AI 2005)*
   A. Aminotransaminase.
   B. Alkaline phosphatase.
   C. Bilirubin.
   D. Albumin.

224. Air in biliary tract is seen in all except: *(AIIMS 1995)*
   A. Gall stone ileus
   B. Sclerosing cholangitis
   C. Carcinoma gall bladder
   D. Endoscopic papillotomy

225. Treatment of choice for Echinococcus granulosus is.
   A. Albendazole *(NBE)*
   B. Mebendazole
   C. Thiobendazole
   D. Praziquantel

226. Bland cholestasis is caused by all of the following drugs, except *(PGI Dec-04)*
   A. Androgen
   B. OCP
   C. Cyclosporine
   D. Estrogen
   E. Chlorpromazine

## ANSWERS, REFERENCES, EXPLANATIONS AND RELEVANT HIGH YIELD FACTS

### Jaundice

**1. Answer is C (Rotor syndrome):** *Harrisons 15th/257, 16th/240; 17th/ 263 (t-43.1); 18th/p 326 (t:42.1); Robbins 7th/888;*

***Rotor's syndrome is an Autosomal recessive inherited disorder characterized by a defect in biliary excretion leading to conjugated hyperbilirubinemia.***

***Hereditary Hyperbilirubinemias*** Q

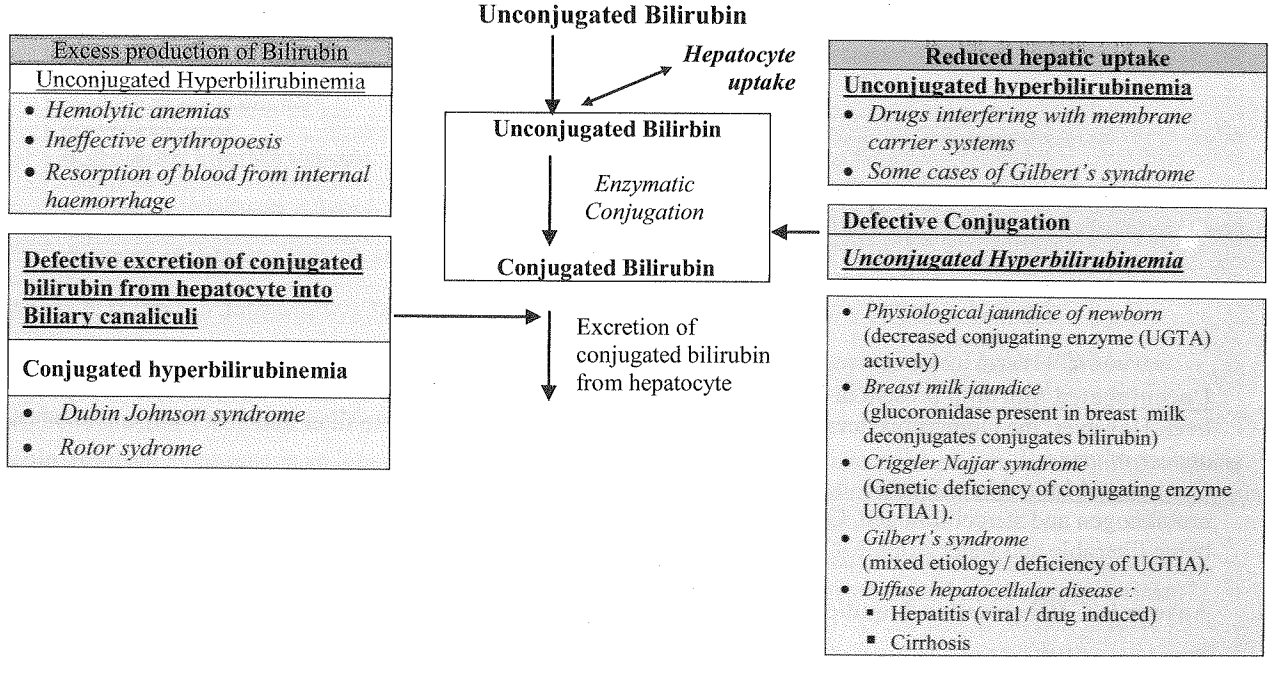
| Unconjugated (defect conjugating enzyme bilirubin glucoronyl transferase) | Conjugated (defect in biliary excretion of conjugated bilirubin) |
|---|---|
| 1. Cirgler Najjar Syndrome type I & type II Q | 1. Dubin Johnson syndrome Q |
| 2. Gilberts syndrome Q | 2. Rotor's syndrome Q |

**Causes of Isolated Hyperbilirubinemia**

| Indirect hyperbilirubinemia | Direct hyperbilirubinemia |
|---|---|
| A. Hemolytic disorders<br>1. Inherited<br>a. Sperocyteosis, elliptocytosis<br>Glucose-6-phosphate dehydrogenase and pyruvate kinase deficiencies<br>b. Sickle cell anemia<br>2. Acquired<br>a. Microangiopathic hemolytic anemias<br>b. Paraoxysmal nocturnal hemoglobinuria<br>c. Immune hemolysis<br>B. Ineffective erythropoesis<br>1. Cobalamin, folate, thalassemia, and severe iron deficiencies<br>C. Drugs<br>1. Rifampicin, probenbecid, ribavirin<br>D. Inherited conditions<br>1. Crigler-Najjar types I and II<br>2. Glibert's syndrome | A. Inherited conditions<br>1. Dubin-Johnson syndrome<br>2. Rotor's syndrome |

**2. Answer is D (Dubin Johnson syndrome):** *Robbin's 7th / 888; Harrison 17th/ 263 Harrison 18th/p 326*

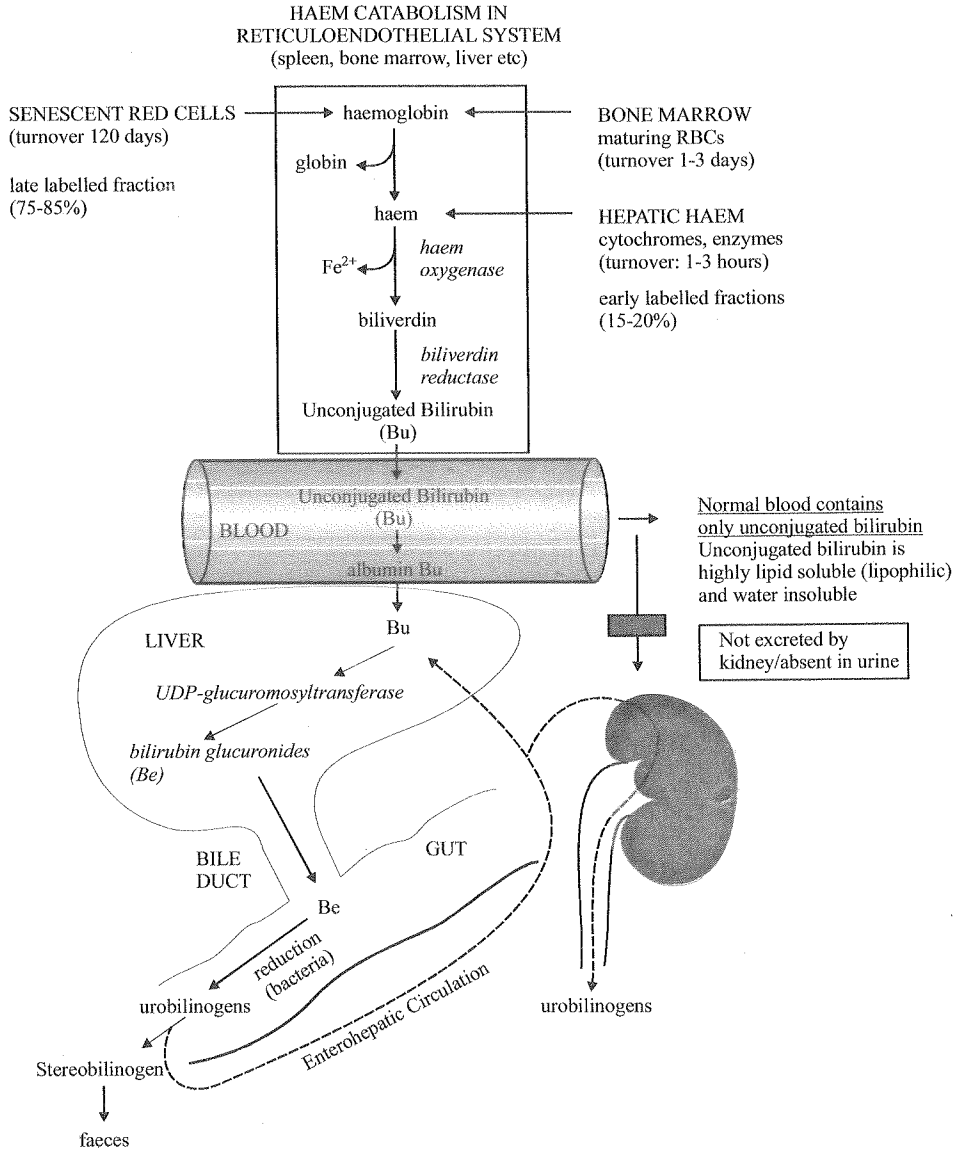
***Dubin Johnson Syndrome results from a hereditary defect in excretion of conjugated bilirubin across the canalicular membrane and leads to conjugated hyperbilirubinemia.***



3. **Answer is C and D (Not filtered and lipophilic)**: *Harrison's 16th/240, 241, 242; 17th/262,263,264; 18th/325, 326, 327*

*Normal urine does not contain bilirubin because normal blood contains bilirubin in the uncongugated form. Unconjugated bilirubin is lipid soluble or lipophilic (water insoluble) because it is transported in the blood as a complex with albumin (albumin-bilirubin complex) which is not allowed to filter through the glomerulus.*

*Although conjugated bilirubin is water soluble and filterable at the glomurulus, conjugated bilirubin is not present in the blood normally and hence does not filter to appear in the urine.*




**Unconjugated bilirubin** present in blood is complexed with albumin to make it soluble in blood and transport it to the liver. However, the glomerulus does not allow the albumin bilirubin complex to filter and *hence bilirubin does not appear in urine.*

**Conjugated bilirubin** is formed in the liver and directly excreted into the GIT through bile where it is reduced to urobilinogen and stercobilinogen. Conjugated bilirubin does not normally circulate in the blood at all and hence despite being filterable and water soluble it does not appear in urine.

4. **Answer is C (Obstructive Jaundice):** *Refer text below*

***Presence of Bilirubin in urine and absence of urinary urobilonogen suggests a diagnosis of obstructive jaundice.***

**Pathophysiology of different types of jaundice**

- Normal blood contains unconjugated bilirubin only (no conjugated bilirubin)

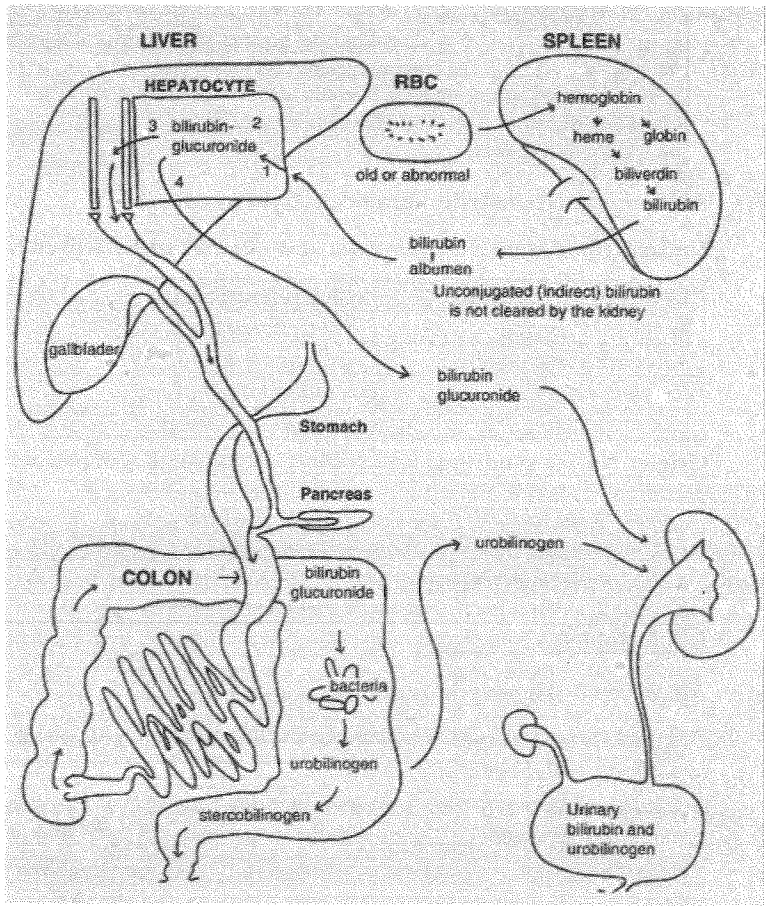
  Unconjugated bilirubin is water insoluble (lipophilic, lipid soluble) and not filterable by the kidney.

- Unconjugated bilirubin is taken up from the systemic circulation by hepatocytes (1)
- Unconjugated bilirubin is then conjugated to bilirubin glucoronide by glucoronyl transferase within the hepatocytes(2)
- Conjugated bilirubin is then excreted into the bile from where it reaches the GIT (3) This is the rate limiting step.

  Conjugated bilirubin is water soluble and filterable by the kidney
  **Normally,** there is no conjugated bilirubin in the systemic circulation and hence no bilirubin is filtered in the kidney or present in the urine.
  **Abnormally**
  When there is hepatocellular dysfunction or bile flow is totally obstructed, conjugated bilirubin "leaks" into the systemic circulation This conjugated bilirubin may now be excreted by the kidney and be detected in urine.
  **Bilirubin in urine (bilirubinuria)**
  Presence of bilirubin in urine suggests a diagnosis of conjugated hyperbilirubinemia either due to hepatocellular jaundice or obstructive jaundice.

- Within the GIT conjugated bilirubin is degraded/reduced to urobilinogen and then to stercobilinogen

  Urobilinogen is water soluble and filterable by the kidney
  **Normally,** a small portion of the urobilinogen is reabsorbed from the gut and excreted by the kidney (<4 mg/day)
  **In non obstructive hyperbilirubinemia (hemolytic, hepatocellular)** the amount of urobilinogen exreated by the kidney is increased as more urobilinogen is formed and reabsorbed.
  ***Elevated levels of urobilinogen suggest primarily an non obstructive hyperbilirubinemia***
  **In obstructive hyperbilirubinemia**, conjugated bilirubin does not reach the GIT and hence no urobilinogen is formed
  ***Absent levels of urobilinogen suggest a diangnosis of obstructive hyperbilirubinemia***




| Condition | Serum Bilirubin | Urine Urobilinogen | Urine Bilirubin | Fecal urobilinogen |
|---|---|---|---|---|
| Normal | Direct 0.1-0.4 mg/dl<br>Indirect 0.2-0.7 mg/dl | 0-4 mg/24 h | Absent | 40-280 mg/24h |
| Hemolytic anemia | ↑ Indirect | Increased | Absent | Increased |
| Hepatitis | ↑ Direct and indirect | Decreased if micro-obstruction is present | Present if microobstruction occurs | Decreased |
| Obstructive jaundice | ↑ Direct | Absent | Present | Trace to absent |

**5. Answer is D (Dubin Johnson Syndrome):** *Harrison 18th/p 325, 326 Harrison's 17th/263, 264, 262*

***Dubin Johnson syndrome is associated with conjugated hyperbilirubinemia & not unconjugated hyperbilirubinemia.***
*Dubin Johnson Syndrome results from a hereditary defect in excretion of conjugated bilirubin across the canalicular membrane and leads to conjugated hyperbilirubinemia.*

**Dubin Johnson** syndrome is an inherited disorder charachterized by defective excretion of conjugated bilirubin from hepatocytes into biliary canaliculi. It thus presents with a clinical picture similar to obstructive jaundice with conjugated hyperbilirubinemia and absence of urobilinogen in urine.

**Hemolytic Anemia** typically presents with unconjugated hyperbilirubinemia and elevated urinary urobilinogens.
**Gilberts syndrome and Crigler Najjar syndrome** also present with unconjugated hyperbilirubinemia. Urinary Urobilinogens are however not elevated in these conditions. *Urobilinogen may never the less be present in urine (N or ↓) in these conditions*

***Hereditary Hyperbilirubinemias*** [Q]

| Unconjugated (defect in conjugating enzyme bilirubin glucoronyl transferase) | Conjugated (defect in biliary excretion of conjugated bilirubin) |
|---|---|
| 3. ***Cirgler Najjar Syndrome type I & type II*** [Q] | ***Dubin Johnson syndrome*** [Q] |
| 4. ***Gilberts syndrome*** [Q] | Rotor's syndrome [Q] |

**6. Answer is A (Hemolytic Jaundice):** *Refer text below*

***Unconjugated Hyperbilirubinemia with elevated urobilinogen levels of urine is characteristic of Hemolytic anemia***

| Condition / syndrome | Hyperbilirubinemia | Urinary Urobilinogen *(N=0-4 mg/24 hrs)* |
|---|---|---|
| *Hemolytic Anemia* | *Unconjugated (Indirect)* | *Increased* |
| *Gilbert's syndrome* | *Unconjugated (Indirect)* | *Normal or Decreased* |
| *Crigler Najjar* | *Unconjugted (Indirect)* | *Normal or Decreased* |
| *Dubin Johnson's* | *Conjugated (Direct)* | *Absent* |

**Crigler Najjar syndrome and Gilbert's syndrome** also present with unconjugated hyperbilirubinemia, however urobilinogen levels are not increased in these conditions.

*Gilberts syndrome and Crigler Najjar syndrome are enymatic disorders charachterized by defective conjugation. These disorders may present with a picture similar to hemolytic jaundice with unconjugated hyer bilirubinamia, with the following exceptions.*
*a. Haemoglobin is not decreased*
b. *Urobilinogen is not increased (Normal or Decreased)*

**Dubin Johnson Syndrome** presents with conjugated hyperbilirubinemia and absent urobilinogen in urine

**7. Answer is B (Hemolytic Jaundice):** *Harper 27th/292*

***Combination of increased urinary urobilinogen and absence of bilirubin in urine is suggestive of hemolytic jaundice or unconjugated hyperbilirubinemia.***

*A similar picture may also be seen in hepatitis but it is more charachteristic of hemolytic jaundice which is the single best answer of choice*

| Condition | Serum Bilirubin | Urine Urobilinogen | Urine Bilirubin | Fecal urobilinogen |
|---|---|---|---|---|
| Normal | Direct 0.1-0.4 mg/dl<br>Indirect 0.2-0.7 mg/dl | 0-4 mg/24 h | Absent | 40-280 mg/24h |
| Hemolytic anemia | ↑ Indirect | Increased | Absent | Increased |
| Hepatitis | ↑ Direct and indirect | Decreased if micro-obstruction is present | Present if microobstruction occurs | Decreased |
| Obstructive jaundice | ↑ Direct | Absent | Present | Trace to absent |

**8. Answer is A (Haemolytic jaundice):** *Harrisons 15th/256, Harrison 16th/238 Read text below; Harrison 17th/ 262, 263, 264*

***All findings in the question corroborate with a haemolytic picture.***

- *Presence of Urobilinogen in urine rules out an obstructive cause for jaundice.*
- *Decrease in haemoglobin and elevated bilirubin levels are consistent with a haemolytic cause.*
- *Gall stones can be explained by precipitation of bilirubin (Bilirubinate crystals)*

**Distinguishing features between various forms of Jaundice :**

| Parameter | Hemolytic | Hepatocellular | Obstructive |
|---|---|---|---|
| **Blood** | **Blood** | **Blood** | **Blood** |
| Haemoglobin (12-18 g/dl) | Decreased | N. | N. |
| Unconjugated bilirubin (0.2 to 0.7 mg/dl) | ↑↑ | N or ↑ | N |
| Conjugated bilirubin (0.1 to 0.3 mg/dl) | N | ↑ | ↑ |
| Alkaline phosphatase (3-13 KAU) (30 to 120 IU/L) | N | N or ↑ | ↑↑ |
| Aminotransferases | N | ↑↑ | N |
| Cholesterol | N | N | ↑ |
| **Stool** | **Stool** | **Stool** | **Stool** |
| Colour of stool | N | N | Pale |
| **Urine** | **Urine** | **Urine** | **Urine** |
| Bilirubin | 0 | ↑ | ↑ |
| Urobilinogen | ↑ | ↑ | ↓ |

**Note :**

- **Gilberts Syndrome and Criggler Najjar syndrome:** are enzyme disorders characterized by defective conjugation. They thus present with a picture similar to Hemolytic with the following exceptions:
  a. Hb is not decreased
  b. Urobilinogen is not increased (N or ↓)
- **Rotor's syndrome and Dubin Johnson syndrome** are characterized by defective excretion.
  They thus present with a picture similar to obstructive with the following exceptions: Alkaline phosphatase is not raised.

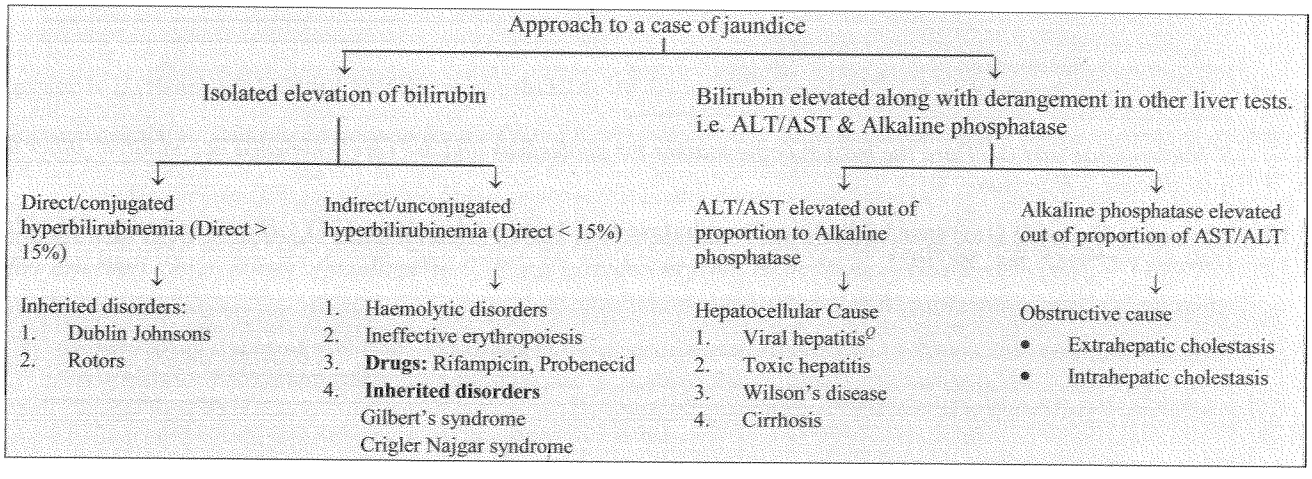
**9. Answer is D (Obstructive jaundice):** *Harrison 15th/256; 16th/240; See previous question; Harrison 17th/ 262, 263*

***The patient in question has high conjugated bilirubin levels (direct bilirubin > 50% of total bilirubin), along with alkaline phosphatase levels more than 6 times normal. The answer of choice therefore is obstructive jaundice.***

**Approach:**
*If direct conjugated bilirubin is greater than 15% of the total bilirubin, it is termed as direct bilirubinemia.*

**A patient presenting with direct bilirubinemia is further approached as follows:**

| Bilirubin | Associated parameter | Inference |
|---|---|---|
| Direct bilirubinemia | Alkaline phosphatase raised out of proportion to transferases (ALT/AST) | Cholestatic obstructive jaundice |
| Direct bilirubinemia | Transferases (ALT/AST) Raised out of proportion to alkaline phosphatase | Hepatocellular jaundice |




**10. Answer is D (Obstructive jaundice):** *Read text below; Harrisons 14th/254, 1664; 15th/256; 16th/240; 17th/ 262, 263; 18th/p 325*

***Direct bilirubinemia (conjugated biriribin > 15% of total bilirubin) along with high serum alkaline phosphatase (6-7 times normal) suggests the diagnosis of obstructive jaundice.***

| | Normal | Patient | Inference |
|---|---|---|---|
| Total bilirubin (mg/dl) | 0.3 to 1.0 | 21.0 | Direct bilirubin is 45% of total bilirubin |
| Conjugated bilirubin (mg/dl) | 0.1 to 0.3 | 9.6 | **Direct bilirubinemia** |
| Alkaline phosphatase | 3-13 KAV | 84 KA | Alkaline phosphatase is raised by atleast six times: **Significant rise** |

***Rise in conjugated bilirubin level*** *may be seen with both, hepatocellular disease (Viral/ infective Hepatitis) and Obstructive jaundice but association with significantly elevated ALP limits our diagnosis to obstructive damage.*

***Rise in alkaline phosphatase levels***

Patient with **parenchymal disease of liver** i.e. hepatocellular disorders : *may show increase in alkaline phosphatase levels but the increase is only slight to moderate and usually not more than two times normal*

**Obstructive lesion:** *Striking increase in alkaline phosphatase* is more suggestive of an obstructive lesion

*In the given question rise in alkaline phosphatase is about 6 to 7 times normal and thus is more in favour of an obstructive cause.*

**11. Answer is A, B, C (85% of the total should be indirect, Hemolytic anemia, Seen in ↑ hemoglobin destruction (↑ bilirubin production):** *Harrison's 17th/262*

***Unconjugated Hyperbilirubinemia is associated with > 85% indirect bilrubin or less than 15% of direct bilirubin. Hemolytic disorders and increased hemoglobin destruction cause unconjugated or indirect hyperbilirubinemia.***

***Biliary atresia and neonatal hepatitis lead to conjugated hyperbilirubinemia.***

Hyperbilirubinemia

| Unconjugated Hyperbilirubinemia | Conjugated Hyperbilinubinemia |
|---|---|
| Direct bilirubin < 15%<br>Indirect bilirubin > 85% | Direct bilirubin > 15%<br>Indirect bilirubin < 85% |
| *Hemolytic anemia and increased hemolysis would lead to unconjugated Hyperbilirubinemia* | *Biliary Atresia would lead to obstructive jaundice with conjugated hyperbilirubinemia* |

**12. Answer is D (Cholestatic disorders) :** *Harrison 16th/1815*

***5' Nucleotidase reflects cholestasis and is rarely elevated in conditions other than liver disease.***

| Most important enzymes reflecting cholestasis |
|---|
| • Alkaline phophatase<br>• 5' Nucleotidase<br>• Gamma Glutanym transpeptidase |

*5' Nucleotidase and GGT are the most specific marker for cholestasis and are rarely elevated in conditions other than liver disease – Harrison*

**13. Answer is C and D (Increased Alkaline Phosphatase and Increased gamma GT) :** *Harrison 18th/p 325, 326, 327 Harrison's 17th/262, 263, 264, 1925*

*Abnormal excretory function of hepatocytes leads to cholestasis.*

***Enzymes that are used to reflect cholestasis may thus be used to assess the excretory function of hepatocytes indirectly. These enzymes include Alkaline phosphatase, 5' nucleotidase and gamma glutamy transferase (GGT)***

Liver Enzymes

| Enzymes that Reflect damage to Hepatocytes | Enzymes that Reflect Cholestasis |
|---|---|
| ALT (SGPT)<br>AST (SGOT)<br>LDH | • Alkaline Phosphatase (AIP)<br>• 5' Nucelotide (5' N)<br>• Gamma Glutamyl Transferase |
| ***ALT*** *is found primarily only in the liver and is hence more specific than AST.*<br>***AST*** *is found in several other tissues besides liver including heart muscle, kidney brain, pancreas, lungs leucocytes and erythrocytes.* | *ALP and 5'N are more specific than GGT.* |

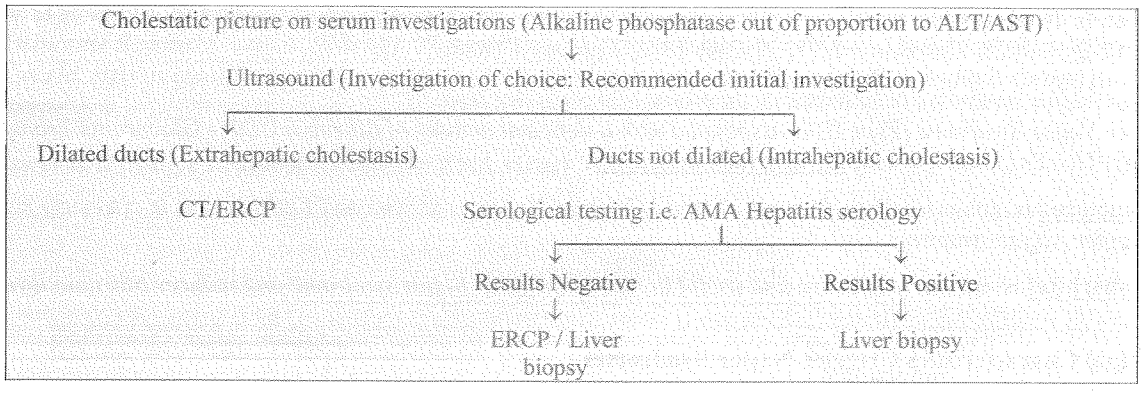
*Note that true assessment of hepatic excretory function requires measurement of serum concentration of substances metabolized and transported by the liver or by determination of rate of clearance of exogenously administered dyes or drugs such as indocyanine green, caffeine, lidocaine and PABA.*
*Liver enzymes including those reflecting cholestasis are not true measures for detecting excretory function of hepatocytes. However, amongst the options provided these are the best answers of exclusion as they may provide an indirect assessment of excretory function of hepatocytes.*

**14. Answer is D (Cholestatic jaundice)**

**15. Answer is A (Ultrasound):** *Harrisons 16th/240 (fig 38-1); see below; Harrison 17th/ 263, 264 Harrison 18th/p 325*

***Initial investigation of choice in a case of obstructive jaundice is: ULTRASONOGRAPHY***
*The patient in question has an obstructive form of jaundice, as is indicated by marked elevation of conjugated bilirubin together with a significant rise is Alkaline phosphatase. Patient: should therefore be next subjected to ultrasonography to confirm the diagnosis and if possible locate the site of block.*

**Protocol for investigating a patient with cholestatic serum profile.**




**16. Answer is B (Bromsulphalein / Sulfobromophthalein) :***Harrison 16th / 1821; 17th/ 1930 Harrison 18th/p 2535, 2536*

***The appearance of late rise in plasma level of Bromsulphalein, BSF / Sulfobromophthalein in the clearance of this dye has been considered as a pathognomic sign of Dubin Johnson syndrome***
***– Metabolism of Bromsulphalein in D-J syndrome; Digestive diseases and Sciences Vol/17 numbers 6.***

***Patients with D - J syndrome exhibit a characteristic rise in plasma concentration of Bromsulphalein at 90 minutes after injection due to reflux of conjugated BSP into circulation from Hepatocyte.*** *– Harrison*

| **Bromsulphalein test for Dubin Johnson syndrome :** *Harrison 16th / 1821* |
|---|
| • *Dubin Johnson syndrome is characterized by a Familial / Autosomal Recessive defect in Hepatic excretory function (from hepatocyte to biliary canaliculi )* |
| • *Biliary excretion of a number of anionic compounds is compromised including that of sulfobromphthalein (Bromsulphalein, BSP), a synthetic dye (cholecystographic agent).* |
| • *To test for D – J syndrome, the role of disappearance of BSP from plasma is determined after its bolus intravenous administration.* |
| • *Patients with D - J syndrome exhibit a characteristic rise in its plasma concentration at 90 minutes after injection due to reflux of conjugated BSP into circulation from Hepatocyte. – Harrison* |

**Dubin Johnson Syndrome : Review**
During Johnson syndrome is an ***autosomal recessive***[Q] hereditary disorder presenting with ***conjugated hyperbilirubinemia***[Q] due to ***defect in hepatic excretory function across the canalicular membrane of hepatocyte.***[Q]

| **Clinical presentation** |
|---|
| • Most patient are asymptomatic (subclinical chemical hyperbilirubinemia) |
| • ***Unexplained low grade jaundice during teenage years Often exacerbated by :*** |
| – ***Oral contraceptive use*** |
| – Pregnancy |
| – Intercurrent illness |
| • Physical examination is usually normal (occasional patient may have hepatosplenomegaly) |
| **Laboratory studies** |
| • ***Conjugated Hyperbilirubinemia*** : Total bilirubin is ***typically between 2 – 5 mg/dl*** *(34 – 85 µmol/L)* *May occasionally be Normal or as high as 20-25 mg/dl(340-430 µmol/L)* |
| • **Bilirubinuria** : Typically present as hyperbilirubinemia is conjugated |
| • ***Other Routine Liver Function Tests including Serum Transaminases and Alkaline Phosphatase are essentially Normal*** |

| Diagnosis | |
|---|---|
| **Bromsulphalein test** : *Elaborated above*<br><br>**Corporphyrin test**<br>**(Preferential urinary excretion of corporphyrin-I)**<br>Corporphrins are byproducts of heme biosnthesis<br>There are two naturally occurring corporphyrins – I & III<br>***Normally approx. 75 % of corporpyrin in urine is isomer III***<br>***In urine of patients with D-J Syndrome total corporphyrin content in urine is norma but > 80 % is Isomer I*** | **Histology :**<br><br>Deposition of melanin like pigment occurs in the liver causing ***liver to appear dark or completely black***.<br><br>*Pigment is thought to be derived from epinephrine metabolites that are not excreted normally* |

17. **Answer is B (Recessive trait):** *Schiff's disease of the liver 10th/229; Harrison 18th/p 326, 2533, 2534 Harrison's 17th/262, 263, 1928; Harrison's 16th/239, 240, 1818; Robbins 7th/888*

*Crigger Najjar syndrome is inherited as an autosomal recessive trait.*
*Crigger Najjar Syndrome (Type II) is associated with a deficient activity of Bilirubin UDP - Glucoronyl Transferase activity (UGITAL) and not with* ***diglucornide deficiency****.*

**Kernincterus** *is a characteristic features of type I Criggler Najjar syndrome and Kernincterus is extremely rare in type II Criggler Najjar syndrome.*

**Phenobarbital** *is extremely effective and useful in type II Criggler Najjar syndrome and reduces bilirubin levels by > 25%.*

**Principal Characteristics Criggler-Najjar Syndromes**

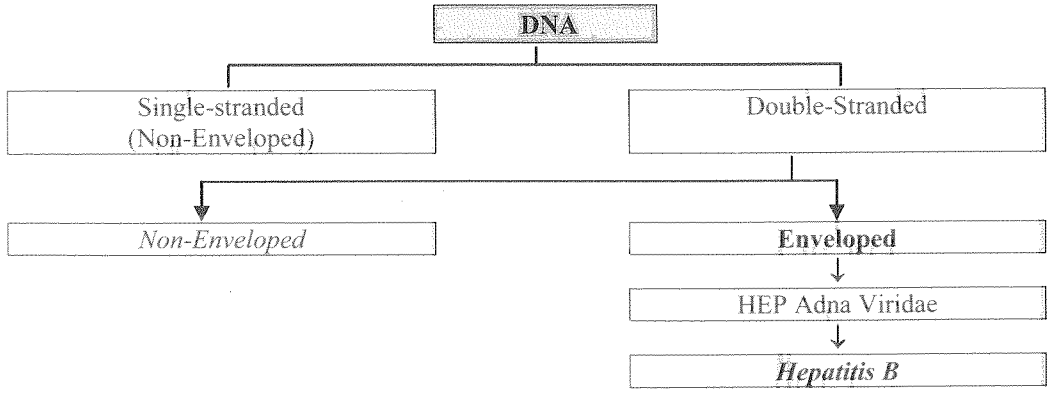
| Feature | Crigler-Najjar Syndrome | |
|---|---|---|
| | Type1 | Type II |
| Total serum bilirubin, μmol/L (mg/dl) | 310-755 (usually > 345)<br>[18-45 (usually < 20)] | 100-430 (usually <345)<br>[6-25(usually <20)] |
| Routine liver tests | Normal | Normal |
| Response to Phenobarbital | None | Decreases bilirubin by>25% |
| Kernicterus | Usual | Rare |
| Hepatic histology | Normal | Normal |
| Bile characteristics | | |
| Color | Pale or colorless | Pigmented |
| Bilirubin fractions monoconjugates | >90% unconjugated | Largest fraction (mean: 57%) |
| Bilirubin UDP-glucuronosyl-transferase | Typically absent; traces in some patients | Markedly reduced:0-10% of normal |
| Inheritance (all autosomal) | Recessive | Predominantly recessive |

## Viral Hepatitis

### General

18. **Answer is A (Double Stranded DNA Virus)**

*Hepatitis B Virus is Double Stranded Enveloped DNA Virus.*



**19. Answer is D (ayw) :** *Manson's Tropical Diseases 23[3d]/116; Atlas of the Liver (Springer) 3[rd]/ 31*

*The most prevalent Hepatitis B in India is Genotype D and a Serotype ayw.*

*HBV is generally classified into 8 genotypes (Genotype A-H) and four serotypes or subtypes (adr, adw, ayr and ayw) based on antigenic determinants of the hepatitis B surface antigen (HBsAg).* ***The most prevalent Hepatitis B in India is Genotype D with a serotype 'ayw'. Genotype A is the second most common reported HBV in India***

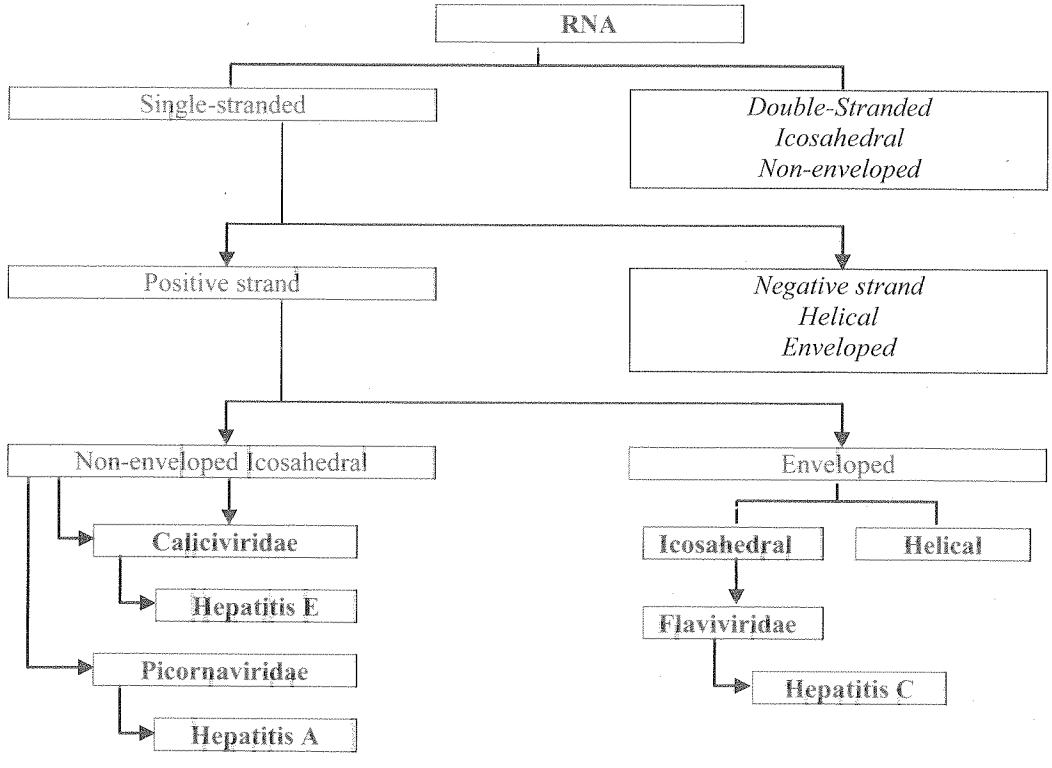
**20. Answer is D (Genotype D) :** Manson's Tropical Diseases 233d/116; Atlas of the Liver (Springer) 3rd/ 31

*The most prevalent Hepatitis B in India is Genotype D (serotype ayw) followed by Genotype A.*

*HBV is generally classified into four serotypes or subtypes (adr, adw, ayr and ayw) based on antigenic determinants of the hepatitis B surface antigen (HBsAg). The prevalence of these serotypes was found to be varied in different parts of the world. HBV is classified in to 8 genotypes (A-H).* ***The most prevelant Hepatitis B in India is Genotype D and a serotype ayw.***

**21. Answer is D (Single stranded Enveloped RNA virus)**

*Hepatitis C Virus is a Single stranded Enveloped (Icosohedral) RNA virus belonging to the family Flaviviridae*




**22. Answer is D (Single Stranded RNA Virus)**

*Hepatitis D virus (HDV) is a single-stranded RNA virus.*

*Hepatitis D virus (HDV) is a small single-stranded circular anti-sense RNA virus with negative polarity that codes for one protein (Delta Antigen). Hepatitis D Virus is dependent on the HBV envelope protein for replication and pathogenicity.*

*Hepatitis D Virus does not fall into any known group of animal viruses. It is the only virus found in humans that has Single Stranded Circular RNA.It resembles Viroids and Satellite viruses.*

23. **Answer is C (Acute viral Hepatitis):** *Harrison 18th/p 2549, 2550, 2530 Harrison's 17th/1926, 1941, 1942*

***Prodromal symptoms of nausea and anorexia, presence of pain in upper abdomen together with characteristic laboratory features (elevated bilirubin, elevated SGOT and SGPT>500 with SGPT > SGOT, and elevated alkaline phosphates to < 3 times normal) suggest the diagnosis of viral hepatitis.***

Diagnosis of Acute viral Hepatitis

| Prodromal Symptoms |
|---|
| ***Anorexia, Nausea, Vomiting***<br>*Fatigue, malaise, arthralgic, myalgia, Fever* |

↓

| Clinical Jaundice and associated Signs |
|---|
| • Clinical Jaundice (Also dark urine, clay coloured stool)<br>• ***Tender Hepatomegaly*** (Right upper abdomen pain/discomfort) |

↓

| Characteristic Laboratory Parameters | | | |
|---|---|---|---|
| Bilirubin | AST/ALT | Alkaline Phosphate | Albumin + Prothrombin time |
| Elevated<br>(Both fractions may be elevated) | Elevated<br>Elevated usually >500 IU/L<br>ALT>AST | Normal to < 3 times normal<br>(N=30 to 120 IU/L)<br>(N=3 to 13 KAU) | Usually normal |

Note:
*ALT is synonymous with SGPT*[Q]
*AST is synonymous with SGOT*[Q]

24. **Answer is C (Acute viral Hepatitis):** *Robbins 7th/899; 'Pathology' by wolf (1998)/572*

***Councilman bodies are acidophilic /eosinophilic apoptotic bodies seen in Acute Viral hepatitis and represent irreversible hepatocyte damage.***

Hepatocyte injury in Acute Hepatitis

| Ballooning degeneration | Cytolysis | Apoptosis (Acidophilic degeneration) |
|---|---|---|
| *Ballooning of Hepatocytes* | *Necrosis of hepatocytes* | ***Councilmann Bodies*** |

25. **Answer is D (HCV):** *Harrison 15th/1728; Harrisons 16th/ 1849, 1829; 17th/ 1945, 1939 Harrison 18th/p 2553, 2546*

***Most common hepatitis to progress to chronicity is Hepatitis C.***

*'Chronic hepatitis follows acute hepatitis in 50-70% of cases. Even in hose with a return to normal in AST/ALT levels after acute hepatitis C, chronic infection is common adding upto 85-90% likelihood of chronic HCV infection after acute hepatitis C.' – Harrison 16th/ 1849*

| Parameter | HAV | HBV | HCV | HDV | HEV |
|---|---|---|---|---|---|
| Progression to chronicity | None | Occasional (1-10%) | Common (50-70%) | *Common | None |

** In acute HBV/HDV co infection, the frequency of chronicity is the same as that for HBV. In HDV superinfection chronicity is variable*

**Clinical and epidemiologic features of viral hepatitis:**

| Features | HAV | HBV | HCV | HDV | HEV |
|---|---|---|---|---|---|
| **Incubation (days)** | 15-45 | 30-180 | 15-160 | 30-180 | 14-60 |
| **Age** | Children, young Adults | Young adults | Any age but more in adult | Any age | Young adults |
| **Transmission** | | | | | |
| *Fecal-oral* | +++ | --- | --- | --- | +++ |
| *Percutaneous* | Unusual | +++ | +++ | +++ | --- |
| *Perinatal* | --- | +++ | + | + | --- |
| *Sexual* | + | ++ | + | ++ | --- |
| **Clinical** | | | | | |
| *Severity* | Mild | Occasionally Severe | Moderate | Occasionally Severe | Mild |
| *Fulminant* | .1% | .1%-1% | .1% | 5-20% | 1-2% |
| *Progression to chronicity* | None | Occasional (1-10%) | Common (50-70%) | Common | None |
| *Carrier* | None $^{Q}$ | 01%-30% | 1.5 to 3.2% | Variable | None $^{Q}$ |
| *Cancer* | None $^{Q}$ | +nt | +nt | Variable | None $^{Q}$ |
| *Prognosis* | Excellent | Worse with age | Moderate | Acute: good Chronic: poor | Good |
| *Prophylaxis* | IgG Vaccine | HBIG Recombinant vaccine | None | - | Unknown |

**Memo :** $^{Q}$ *HCV is the most common Virus associated with transfusion associated hepatitis*
$^{Q}$ *No vaccine / prophylaxis is available for HCV*
$^{Q}$ *Malignant potential is present with HCV (also with HBV)*

**26. Answer is B and C (Hepatitis B and Hepatitis C) :** *Repeat*

*Progression to chronicity is seen with hepatitis B and Hepatitis C*

**27. Answer is C (Hepatitis B):** *Harrison's 15th/ 1748; Harrisons 16th/1829 t; Harrison 17th/ 1939 Harrison 18th/p 2546*

***Perinatal transmission is most significant with hepatitis B***

**Perinatal transmission of various Hepatitis viruses as described in Harrison's Text:**

| Hepatitis virus | HAV | HBV | HCV | HDV | HEV |
|---|---|---|---|---|---|
| Perinatal transmission | - | +++ | - | + | - |

*Perinatal transmission with HCV is seen primarily with HIV co-infection and high level viremia*

**28. Answer is A (Hepatitis E):** *Harrison's 14th/ 1684; 15th/ 1728 t; 16th/1829 t; Harrison 17th/ 1939 Harrison 18th/p 2546*

***Hepatitis B, C and D are essentially spread by parenteral routes.***
***Hepatitis A & E are non parenteral hepatitis.***

**29. Answer is D (LKM2 – Chronic Hepatitis D):** *Harrison's 17th/1968; 'Hepatobiliary Tract & Pancreas' by Reddy (Mosby) 1st (2004)/145; 'Self Assessment Colour Review of Hepatobiliary Medicine' 1st/150 (Q144)*

***Hepatitis D is associated with Anti LKM3 Antibodies and not Anti LKM2 antibodies***

**Anti-Liver Kidney Microsomal Antibodies (anti-LKM antibodies)**

*Anti-Liver Kidney Microsomal (LKM) antibodies* are detected in the sera of patients with different types of acute or chronic liver disease.

These antibodies are target against *Cytochrome P-450 components (antigens)*

*Three types of LKM antibodies* have been most extensively studied

| Microsomal Antibodies | Antigen | Disease |
|---|---|---|
| ***Anti-LKM1*** | Cytochrome P450 2D6 | • ***Autoimmune Hepatitis type II***<br>• ***Chronic Hepatitis C (10%)*** |
| ***Anti-LKM2*** | Cytochrome P450 2C9 | • ***Drug induced Hepatitis***<br>(Tienilic acid induced Hepatitis) |
| ***Anti-LKM3*** | Cytochrome P450 1A2 | • ***Chronic Hepatitis D*** |

**30. Answer is D (HDV/HBV Superinfection):** *Harrison 18th/ 2546*

***HDV superinfection of chronic Hepatitis B is associated with a 20 percent risk of progression to fulminant hepatitis and Acute Hepatic Failure.***

| Feature | HAV | HCV | HEV | HBV |
|---|---|---|---|---|
| *Fulminant Infection (Acute Liver Failure)* | *0.1%* | *0.1%* | *1-2 %*<br>*HEV in pregnant Women: 20%* | *HBV : 1 %*<br>*HBV/HDV Co-infection : 5 %*<br>*HDV/HBV Superinfection: 20 %* |

***Tendency to cause acute liver failure (fulminant infection) is highest with HDV Superinfection on Chronic Hepatitis B and Hepatitis E infection in pregnant women (up to 20 percent)***

***Note:***

- *Hepatitis E is the most common cause of Acute Liver Failure in India*
- *Hepatitis B remains the most common viral agent responsible for Acute Liver Failure Worldwide*
  - *Although Hepatitis E has a higher tendency to cause fulminant infection (1-2 %) in comparison to Hepatitis B infection (Up-to 1%), Hepatitis B is the most common cause of fulminant infection overall since the overall incidence of Hepatitis B Hepatitis is higher than the incidence of Hepatitis E Hepatitis*
- *Tendency to cause acute liver failure (fulminant infection) is highest with HDV Superinfection on Chronic Hepatitis B and Hepatitis E infection in Pregnant women (up to 20 percent)*

**31. Answer is D (HDV super-infection on HBV):** *Harrison's 18th/2552*

***HDV superinfection of a person with chronic Hepatitis B (HBV) has the worst prognosis with high likelihood of fulminant hepatitis and death.***

*'Among patients ill enough to be hospitalized for acute hepatitis B infection the case fatality rate is 1%. Patients with simultaneous acute hepatitis B and hepatitis D do not necessarily experience a higher mortality rate than do patients with acute hepatis B alone, however in several recent outbreaks of acute simultaneous HBV and HDV infection amongst injection drug users the case fatality rate has been ~ 5%.* ***In the case of HDV super infection of a person with chronic hepatitis B, the likelihood of fulminant hepatitis and death is increased substantially. In out breaks of severe HDV super infection in isolated populations with a high hepatitis B carrier state the mortality has been recorded in excess of 20%*** *- Harrison's 18th/2552*

| Prognosis in HBV Infection |
|---|
| *Acute HBV infection ≤ simultaneous HBV – HDV confection << HDV super-infection on HBV infection*<br>*(Best prognosis)* *(worst prognosis)* |

## Hepatitis B

**32. Answer is B (IgM antibody to $Hb_c$ Ag):** *Read text below; Various texts; Harrison 18th/p 2550, 2551, 2539, 2540; Harrison 17th/ 1933, 1934, 1943, 1944*

***Acute infection is best indicated by an IgM anti $Hb_c$ Ag.***

**Serology of Hepatitis B**

| | HBSAg | Anti HBsAg | HBe Ag | Anti HBeAg | Anti HBcAg |
|---|---|---|---|---|---|
| Acute HBV (with high infectivity) | + | - | + | | IgM |
| Acute HBV (with low infectivity) | + | - | | + | IgM |
| Chronic HBV (High infectivity) | + | - | + | | IgG |
| Chronic HBV (low infectivity) | + | - | | + | IgG |

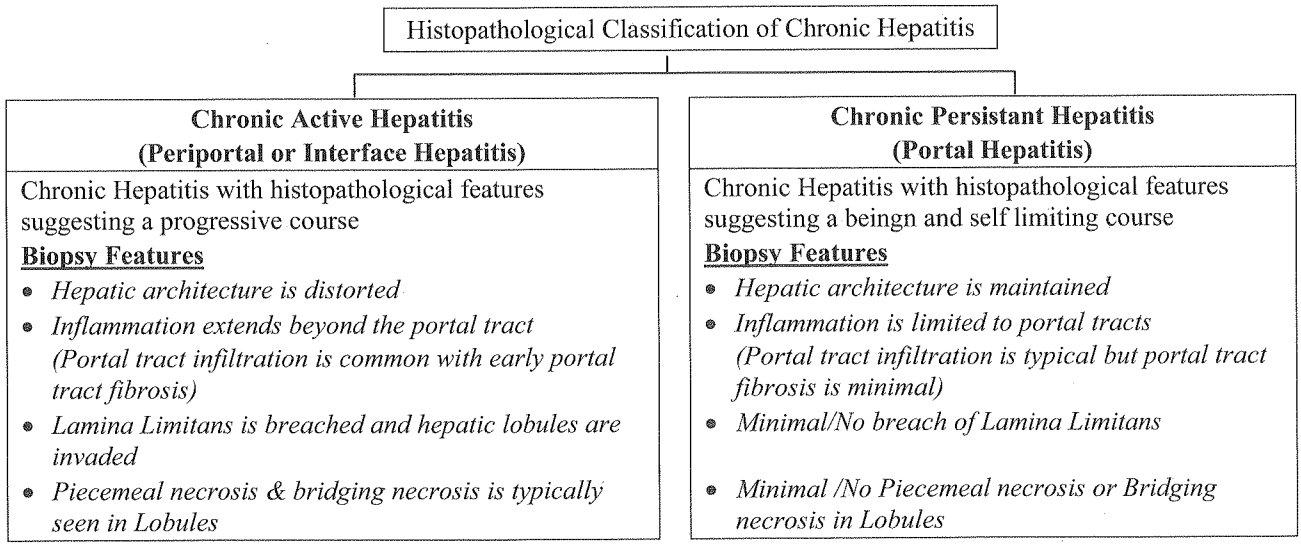
*Hbs Ag would be positive even in chronic infection and hence cannot be used to establish a diagnosis of acute Hepatitis B infection.*

| Hbs Ag | Anti Hbs Ag |
|---|---|
| Indicates that the person is infected with the virus. The infection may manifest as 'disease' either acute or chronic, or be just present as in carrier state<br>Hbs Ag thus indicated as possible:<br>- Acute disease<br>- Chronic disease<br>- Carrier state | With the development of antibody to Hbs Ag i.e. Anti Hbs Ag, the Hbs Ag antigen disappears from the serum<br>- Patient is immune (with immunization Antibody develops and Hbs Ag disappears)<br>- Patient is protected<br>Anti Hbs Ag indicates good immunity ♀<br>Anti Hbs Ag indicates protection against Hepatitis B ♀ |
| **Hbc Ag** | **Anti Hbc Ag** |
| It is a hidden component of the viral core and is not detectable at all | Antibodies to Hbc Ag develop early in the course of disease<br>Anti Hbc Ag is the first antibody to appear after an acute infection and persists in serum even during the recovery phase<br>- When acute antibody is of IgM type<br>- When chronic antibody is of IgG type |
| **Hbe Ag** | **Anti Hbe Ag** |
| Denotes high infectivity ♀ and active disease | Denotes low infectivity |

***Window period*** is a period during recovery phase when both of these are negative and the diagnosis may be missed if test includes only Hbs Ag and Anti Hbs Ag.

**33. Answer is C (Histopathology):** *Textbook of pathology by Dutta (Jaypee) 2nd/755; 'Biopsy Interprelation of Liver' by Geller & Petrovic (Lippincott Williams) 2nd/108*

***Chronic Active Hepatitis and Chronic Persistant Hepatitis (CPH) are histopathological classification systems for various forms of chronic hepatitis based on findings on biopsy specimens.*** *This classification system is however obsolete now and should not be used.*




**34. Answer is D (Fecal-oral route):** *Harrison's 18th/2546*

***Hepatitis B is not transmitted through fecal-oral route (stool).***

**Transmission of Viral Hepatitis:**

| Feature | HAV | HBV | HCV | HDV | HEV |
|---|---|---|---|---|---|
| **Transmission** | | | | | |
| Fecal-oral | +++ | – | – | – | +++ |
| Percutaneous | Unusual | +++ | +++ | +++ | – |
| Perinatal | – | +++ | ± | + | – |
| Sexual | ± | ++ | ± | ++ | – |

35. **Answer is D (90%):** *Harrison's 18th/2547*

***The rate of perinatal transmission of hepatitis B (HBV) essentially depends on the presence or absence of HBe Ag and viral replication. The rate of perinatal transmission of HBV may be as high as 90% in neonates born to mothers who are positive for HBe AG.***

*'The likelihood of perinatal transmission of HBV correlates with the presence of HBe Ag and high level viral replication.* ***90% of HBe Ag positive mothers*** *but only 10-15% of Anti-HBe Ag negative mothers transmit HBV to their offspring' - Harrison's 18th/2547*

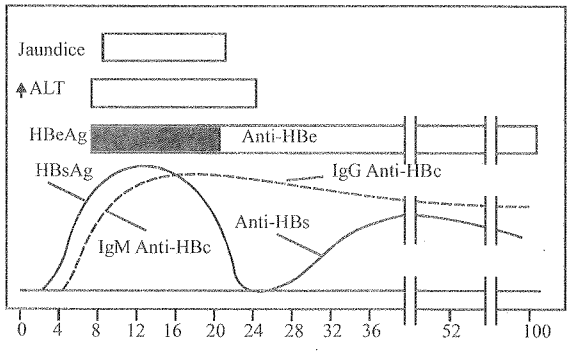
*'Transmission of infection from an HBV carrier mother to her neonate accounts for the majority of new infections in the world today. Sixty to 90% of Hepatitis B surface antigen (HBs Ag) positive mothers who are Hepatitis B 'e' antigen (HBe Ag) positive transmit the disease to their offspring, whereas mothers who are positive for antibody to HBe Ag (Anti - HBe) do so less frequently (15-20%). - Sleisenger & Fordtran's Gastrointestinal & Liver Disease 8th/1647*

36. **Answer is A (HBs Ag):** *Harrison 14th/ 1679, Harrison 15th/ 1721; Harrison 16th/1825; Harrison 17th/ 1933, 1934, 1943 Harrison 18th/p 2539, 2550, 2551*

***The earliest marker appearing in serum in acute Hepatitis B infection is HBs Ag.***

- ***After infection the first virological marker detectable in serum is – HBsAg*** Q ***– Harrisons 16th***
  - it precedes elevation of serum aminotransferases as well as clinical symptoms. Q
  - it remains elevated during the entire icteric or symptomatic phase of acute hepatitis B & beyond. Q

  Anti Hbs Ag appears only after Hbs Ag has disappeared (occasionally after a gap of several weeks).
- **IgM Anti HBcAg** is demonstrable in serum *beginning within 1-2 weeks after the appearance of HBsAg.* Q
  HBcAg is sequestrated and not detectable routinely in the serum. Q
- **Anti HBe Ag** appears shortly before disappearance of Hbs Ag.
  HBeAg appear concurrently or shortly after HBsAg Q. This too is detectable during the acute phase.

| Scheme of typical clinical and laboratory features of acute viral hepatitis B | Sequential |
|---|---|
|   | ***Hbs Ag*** ↓ ***Hbc Ag*** ↓ ***Anti Hbc Ag (IgM)*** ↓ ***Anti Hbc Ag*** ↓ ***disappearance of Hbs Ag and*** ↓ ***appearance of anti Hbs Ag.*** |

**37. Answer is B (Presence of IgM anti-HBc in serum):** *Harrison 16th/ 1833; 17th/ 1933, 1934 Harrison 18th/p 2539, 2540*

***Although Hbs Ag is the earliest virological marker in serum of patients with acute viral hepatitis B, it does not help in establishing the diagnosis of acute Hepatitis B infection.*** *This is so because presence of Hbs Ag only denotes the fact that the patient is a carrier of the above infection and such a patient may well be a case of chronic hepatitis B.*
*It is the presence of IgM anti HBc that confirms an acute hepatitis B infection.*

| Diagnostic interpretation | HBs Ag | IgM Anti HBc |
|---|---|---|
| Acute hepatitis B infection | + | + |
| Chronic Hepatitis B infection | + | - |
| Acute Hepatitis B infection (Below Hbs Ag detection threshold) | - | + |

As is evident from the above chart, ***the basis of diagnosis of acute Hepatitis B infection is either presence of both Hbs Ag & anti HBc IgM or only IgM anti HBc. Presence of HBs Ag alone cannot be used in establishing the diagnosis of acute hepatitis B infection.***

**38. Answer is A (IgM Anti HBc Antibody):** *Harrison 18th/2539, 2540, 2544 Harrison's 17th/1938, 1934, 1943; Harrison's 16th/1823, 1824, 1833; Hepatology Principles and Practice by Kuntz 2nd /117*

*IgM Anti HBc Antibody is the most reliable marker of acute HBV infection.*

*IgM Anti HBc Antibody is known to be the most reliable marker of an acute HBV infection since it is detectable even during the so called serological gap and is charachteristically absent in chronic infections (IgG HBc Antibody is present in chronic infections)-Hepatology: Principles and Practice' 2nd/117*

| | HBsAg | HBeAg | IgM anti-HBc | IgG anti-HBc | Anti-HBs | Anti-HBe | HBVDNA | Interpretation |
|---|---|---|---|---|---|---|---|---|
| Acute HBV Infection | + | + | + | | - | | +++ | Early phase |
| | - | - | + | | - | + | + | Window phase |
| | - | - | - | + | + | + | ± | Recovery phase |
| Chronic HBV Infection | + | - | - | + | - | + | ± | Inactive carrier state |
| | + | - | - | + | - | + | ++ | HBeAg-chronic hepatitis |
| | + | + | - | + | - | - | +++ | HBeAg+chronic hepatitis |

**HbsAg**, hepatitis B surface antigen;**HBeAg**, hepatitis B e antigen;**IgM**, immunoglobulin M;**anti-HBc**, hepatitis B core Antibody; **IgG**, immunoglobulin G; **anti-HBs**, hepatitis B surface antibody; **anti-HBe**, hepatitis B e antibody

**39. Answer is C (IgM anti-HBc):** *Harrison 16th/1832, 1833; 17th/ 1932, 1933, 1935; 18th/2538, 2539, 2540, 2541*

***Hbs Ag*** is present in recent hepatitis B infection but it ***is not specific to acute infection*** (*it may also be seen in carriers*).
*IgM anti- HBc is specific for acute or recent hepatitis, and hence is the answer of choice.*

**40. Answer is A (HBe Ag):** *'Hepatology' by Kuntz 3rd/121; Harrison's 17th/1942, 1943, 1944; 'Viral Infections & Treatment' by Weigmann (2003)/225*

*HBe Ag is the most important marker for Active Hepatitis B (High infectivity and active disease) amongst the options provided.*

Markers for Active Hepatitis B (Persistent Replication; High Infectivity: Active Disease)

- *HBV DNA*
- *HBV DNA polymerase*
- *HBe Ag*

**Markers for Hepatitis B Virus Replication**

| HBV DNA | HBV DNA Polymerase | HBe Ag levels |
|---|---|---|
| • ***HBV DNA is the most sensitive and specific marker of virus replication*** | • ***HBV DNA polymerase is considered the traditional marker active viral replication*** | • ***HBeAg is considered a convenient and readily detectable qualitative marker of HBV replication and relative infectivity*** |
| • HBV DNA may provide both, a qualitative and quantitative estimate of virus replication | • HBV DNA polymerase activity usually parallel's serum HBV DNA levels | *The HBe Ag if detectable is considered a marker for active viral replication, but the lack of HBe Ag does not exclude viral replication* |
| • *HBV DNA estimation as a measure of virus replication has largely replaced the determination of DNA polymerase* | • Both HBV DNA and HBV DNA polymerase are markers for the complete virion. | |
| • ***The Gold standard for confirmation of viral replication is HBV DNA detection*** | | |

**41. Answer is A (Indicates Viral Replication and Infectivity)** *: Repeat*

*HbeAg is a qualitative marker for Hepatitis B virus Replication and its detection in the serum indicates high infectivity and active disease.*

**42. Answer is D (AST & ALT) :** *'Hepatology' by Kuntz 3rd/121; Harrison's 17th/1942, 1943, 1944; Harrison 18th/p 2549, 2550, 2551, 2552 'Viral Infections & Treatment' by Weigmann (2003)/225*

*AST & ALT levels are not considered markers for active viral replication.*

*HBV DNA, HBV DNA polymerase and HBeAg levels are all considered markers for active viral replication, with HBV DNA being the most sensitive marker (gold standard)*

**43. Answer is A (HBV DNA):** *Refer previous question*

*HBV DNA is the most sensitive marker of active Hepatitis B virus replication*

*'HBV DNA is the most sensitive marker of virus replication. The detection of HBV DNA as the most sensitive marker of virus replication end as such proof of infectivity has replaced the determination of DNA polymerase'*
*– 'Hepatology' by Kuntz 3rd/121*

*'The gold standard for confirmation of viral replication is qualitative HBV DNA detection'*
*– 'Viral Infections & Treatment' by Weigmann (2003)/225*

Markers for HBV Replication
***HBV DNA$^{Q}$ > HBV DNA polymerase$^{Q}$ > HBe Ag$^{Q}$***

**44. Answer is A and D (HBsAg and IgM anti – HBc) :** *Harrison 18th/p 2550 Harrisons 17th/1943*

*Acute Hepatitis B is characteristically diagnosed by the presence of IgM anti HBc with HBs Ag. Presence of IgM anti HBc without HBs Ag may suggest acute hepatitis in the window period.*

| HbsAg | Anti-HBs | Anti-HBc | HBeAg | Anti-HBe | Interpretation |
|---|---|---|---|---|---|
| + | - | ***IgM*** | + | - | Acute Hepatitis B, high infectivity |
| - | - | ***IgM*** | +/- | +/- | 1. Acute Hepatitis B<br>2. Anti—HBc "window" |

**45. Answer is None:** *Harrison 18th/p 2550, 2551 Harrison's 17th/1944, 1943; Harrison's 16th/1823, 1824*

*The next best investigation to confirm the diagnosis of acute hepatitis B infection should be serological measurement of IgM anti, HBc antibody, which is not provided amongst the options (probably HBc Ag has been misprinted as HBeAg)*

*Neither of the options provided (HBeAg, Anti HbeAg, antiHBeAg (Igm) or HBV DNA) can confirm a diagnosis of Acute Hepatitis.*

**46. Answer is A (Acute Hepatitis B)**

***The serum profile of the patient suggests Acute Hepatitis B with High Infectivity.***

*Positivity for HBsAg and IgM type antibodies against HbC indicates Acute Hepatitis B. The presence of HBeAg further indicates High Infectivity.*

**47. Answer is B (Acute hepatitis B infection with high infectivity):** *Harrisons 16th/1832, 1833; Harrison 17th/ 1935, 1942, 1943, 1944 Harrison 18th/p 2540, 2550, 2551*

*Presence of Anti HB IgM and Hbs Ag indicates acute infection. Presence of Hbe Ag indicates high infectivity*

**48. Answer is B (HBV pre-core mutant):** *Harrison 18th/p 2541, 2542 Harrison's 17th/1935, 1936; 'Blueprints Pocket Gastroenterology' by Grover (Lippincott-Williams) 1st (2007)/115*

*Evidence of chronic active hepatitis B (suggested by elevated liver enzymes) in a patients with detectable HBV DNA but negative HBe Ag suggests a diagnosis of precore mutant chronic hepatitis B*

**Precore mutant chronic hepatitis B**

- Precore mutant form of chronic hepatitis B represents an infection with a molecular variant of the hepatitis B virus that results in an *unusual serologic – clinical profile*.
- ***Such patients have severe chronic hepatitis B infection with detectable HBV DNA levels, but HBe Ag antigen is typically negative***
- This *results from an infection with an HBV mutant that contains an alteration in the precore regions rendering the virus incapable of encoding HBe Ag*
- Patients with such mutations in the precore region are unable to secrete HBe Ag, have a negative HBe Ag phenotype but *tend to have severe liver disease that progresses more rapidly to cirrhosis*
- *Characteristic of such HBe Ag negative (precore mutant) chronic hepatitis B are lower levels of HBV DNA (≤ $10^5$ copies /ml) and one of several patterns of aminotransferase activity – persistent elevation, periodic fluctuation above the normal range and periodic fluctuations between the normal and elevated range*
- *HBe Ag negative chronic hepatitis B with mutation in the pre-core region is now the most frequently encountered form of hepatitis B in the Mediterranean countries and in Europe.*

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**49. Answer is A (Inactive HBV carrier):** *Harrison 18th/p 2550, 2551 Harrison's 17th/1943; 'Blue Prints Pocket Gastroenterology' by Grover (Lippincott) 1st (2007) /114; Hepatitis B Research Advances' by Willis (2007) /12*

***Absence of clinical signs and symptoms of liver damage and normal liver enzymes in an HBs Ag positive individual with otherwise unremarkable serological tests suggests a diagnosis of Inactive HBV carrier state.***

*'An inactive hepatitis B carrier is defined as one with HBs Ag in serum but without HBe Ag with normal liver function tests and with low/ undetectable levels of HBV DNA (< $10^3$-$10^4$ virions/ml) - 'Blue Prints Pocket Gastroenterology' by Grover (Lippincott Williams) 1st (2007) /114*

**Chronic Hepatitis B carriers** *(HBs Ag + ve with IgG Anti HBc)*

Chronic Hepatitis B virus carriers can be divided into two categories based on activity of the virus and evidence of liver damage

**Inactive HBs Ag Carrier state**

- Patients with negligible virus replication (HBV DNA levels $\leq 10^3$ virions/ml) and /or no clinical signs and symptoms of liver damage and normal liver enzyme levels are characterized as inactive HBV carriers
  *Inactive HBV carriers harbor Hepatitis B virus antigen (HBs Ag), but are clinically asymptomatic, have a normal physical examination with normal liver enzymes (AST & ALT). HBe Ag is typically negative and levels of HBV DNA are less than $10^3$-$10^4$ virions/ml*
- Such patients have minimal (if any) liver inflammation or damage, and usually live a normal life. However compared to the general population these patients remain at risk for hepatocellular carcinoma
- Treatment is currently not recommended for Inactive HBV carrier. However *regular observation is advised* as there is a risk for reactivation of virus.

**Chronic Hepatitis B (Active)**

- Patients with active virus replication ( HBV DNA levels > $10^3$ -$10^4$ virions/ml) and /or clinical signs and symptoms of liver damage or elevated liver enzyme levels are characterized as chronic hepatitis B patients.
- Depending on the presence or absence of HBe Ag two type of chronic (active) hepatitis B may be identified.

**HBe Ag positive chronic hepatitis B**

*These HBs Ag positive, individuals are also positive for HBe Ag and show detectable HBV DNA levels. Such patients are in the replicative phase of chronic hepatitis B infection, have persistently or intermittently elevated liver enzymes and liver biopsy results typically reveals inflammation and damage*

Patients with chronic (active) hepatitis B may become inactive (relatively non replicative) over time (rate of ~10 % per year) by becoming negative for HBe Ag and HBV DNA (HBV DNA < $10^3$ - $10^4$) virions/ml) Liver injury tend to subside in such patients and these may then be characterized as 'inactive carriers'

**HBe Ag negative chronic hepatitis B (Precore mutant)**

*Such HBs Ag positive individuals are negative for HBe Ag but show detectable HBV DNA levels. Such patients are also in the replicative phase of chronic hepatitis B (despite negative HBe Ag) and have persistently or intermittently elevated liver enzymes and liver biopsy results typically reveal severe inflammation and damage*

Negative HBe Ag Status *results from a mutant strain of hepatitis B that is characterized by the failure of the virus to make the hepatitis B 'e' antigen (HBe Ag).* This mutation is called the ***'precore' mutation*** as it prevents the translation of a precore protein to prevent HBe antigen production.
*This mutation does not however affect the ability of the virus to replicate*

**50. Answer is A (DNA polymerase):** *Current Diagnosis and Treatment in Infectious Diseases 1st/437*

***DNA polymerase is a marker for active viral replication.***
***DNA polymerase are usually associated with Acute viral hepatitis B when there is active viral replication and hence DNA polymerase is the single best answer amongst the options provided***

*Note that although DNA polymerase is often present in acute Hepatitis B infection, its presence suggests active virus replication (like HbeAg, HBV DNA) and it should not be used as a laboratory marker for acute hepatitis B infection.*

***'During the acute episode of disease when there is active viral replication large amounts of HBsAg and Hepatic B virus DNA can be detected in the serum as can fully developed virions and high levels of DNA polymerase and HBeAg'***-*Current Diagnosis and Treatment in Infections Disease/437*

**51. Answer is A (IgM against core antigen):** *Harrison's 16th/1832; Pathology by Wolf (1998)/582*

***IgM antibody against core antigen is a diagnostic of an acute infection with hepatitis B virus. IgM antibodies against core antigen are characteristically absent in patients with chronic hepatitis B.***
***(Absent in both forms of chronic hepatitis, namely, chronic active hepatitis and chronic persistent hepatitis)***

**Chronic Hepatitis**

| Chronic Persistent Hepatitis **(Low infectivity; HBeAg-ve chronic Hepatitis)** | |
|---|---|
| HBsAg | +ve |
| HBeAg | -ve |
| IgM HBc | -ve |
| HBV DNA | +ve |

| Chronic Active Hepatitis **High infectivity; HBeAg+ve chronic Hepatits** | |
|---|---|
| HBsAg | +ve |
| HBeAg | +ve |
| IgM Anti HBc<br>IgG Anti HBc | -ve<br>+ve |
| HBV DNA | +ve |

**52. Answer is D (Immunized person with hepatitis B vaccine):** *Harrison, 15th/1731; 16th/1832 See previous question; Harrison 17th/ 1943 Harrison 18th/p 2550*

***Isolated Anti-HBs Ag is seen in immunization with HBs Ag.***

Commonly Encountered Serologic Patterns of Hepatitis B Infection:

| HBsAg | Anti-HBs | Anti-HBc | HBeAg | Anti-HBe | Interpretation |
|---|---|---|---|---|---|
| + | – | IgM | + | – | Acute hepatitis B, high infectivity |
| + | – | IgG | + | – | Chronic hepatitis B, high infectivity |
| + | – | IgG | – | + | Late acute or chronic hepatitis B, low infectivityHBeAg–negative ("precore–mutant") hepatitis B (chronic or, rarely, acute) |
| + | + | + | +/– | +/– | 1. HBsAg of one subtype and heterotypic anti–HBs (common)<br>2. Process of seroconversion from HBsAg to anti– HBs (rare) |
| – | – | IgM | +/– | +/– | 1. Acute hepatitis B<br>2. Anti–HBc "window" |
| – | – | IgG | – | +/– | 1. Low–level hepatitis B carrier<br>2. Hepatitis B in remote past |
| – | + | IgG | – | +/– | Recovery from hepatitis B |
| – | + | – | – | – | 1. Immunization with HBsAg (after vaccination)<br>2. Hepatitis B in the remote past (?)<br>3. False–positive |

**53. Answer is A (Vaccination):** *Harrison 18th/p 2550 Harrison 17th/1943*

***Isolated Anti-HBs Ag in serum is seen in immunization with HBs Ag.***

| Possible Causes of Isolated Anti-HBsAg Positivity in serum (Other markers negative) |
|---|
| • Immunization with HBsAg (after vaccination)<br>• Hepatitis B in the remote past (?)<br>• False-positive |

**54. Answer is D (Anti-HBs Ag ):** *Harrison 17th /1943; Harrison's 18th/2550*

***Anti-HBsAg is the only serological marker to appear after immunization with hepatitis vaccine.***

| Diagnostic interpretation | Hbs Ag | Anti Hbs | Anti HBc | Hbc Ag | Anti Hbe |
|---|---|---|---|---|---|
| *Immunization with Hbs Ag*<br>(? Hepatitis B is remote past)<br>(? False positive) | - | + | - | - | - |

***Isolated Anti-HBs Ag in serum is seen in immunization with HBs Ag.***

| Possible Causes of Isolated Anti-HBsAg Positivity in serum (Other markers negative) |
|---|
| • *Immunization with HBsAg (after vaccination)*<br>• *Hepatitis B in the remote past (?)*<br>• *False-positive* |

**55. Answer is B (Anti-HBs):** *Repeat*

***Anti-HBs is the only serological marker to appear after imunization with HBV Vaccine.***

**56. Answer is A (Anti-HBc):** *Harrison's 18th/2550*

***IgM type Anti HBc may be the only serological marker during window period of Hepatitis B.***

*Presence of IgM Anti-HBc without HBs Ag may suggest acute hepatitis B in the window period.*

| HbsAg | Anti-HBs | Anti-HBc | HBeAg | Anti-HBe | Interpretation |
|---|---|---|---|---|---|
| + | - | ***IgM*** | + | - | Acute Hepatitis B, high infectivity |
| - | - | ***IgM*** | +/- | +/- | 1. Acute Hepatitis B<br>2. Anti—HBc "window" |

*Occasionally a gap of several weeks or longer may separate the disappearance of HBsAg and the appearance of Anti-HBs after an acute infection with Hepatitis B virus. During this 'gap' or 'window' period, presence of Anti-HBc may represent the only serological evidence of current or recent HBV infection*

**57. Answer is D (IgM anti HBe):** *Harrisons 16th/ 1833; 17th/1934, 1935, 1942, 1943, 1944; 18th/2539, 2540, 2550, 2551*

***If a clinical diagnosis of acute viral hepatitis (of any type) is suspected, the patient should undergo the following four serological tests.***

1. HBsAg – *To detect hepatitis B infection*
2. IgM Anti HBc – *To detect whether the hepatitis B infection is acute or chronic.*
3. IgM Anti HAV – *To establish the presence of acute hepatitis A infection.*
4. Anti HCV - *To establish the presence of acute hepatitis C infection.*

**Simplified Diagnostic Approach in Patients Presenting with Acute Hepatitis** - *Harrison*

| HbsAg | IgM Anti-HAV | IgM Anti-HBc | Anti-HCV | Diagnostic Interpretation |
|---|---|---|---|---|
| + | - | + | - | Acute hepatitis B |
| + | - | - | - | Chronic hepatitis B |
| + | + | - | - | Acute hepatitis A superimposed on chronic hepatitis B |
| + | + | + | - | Acute hepatitis A and B |
| - | + | + | - | Acute hepatitis A and B (HBs Ag below detection threshold) |
| - | - | + | - | Acute hepatitis B (HbsAg below detection threshold) |
| - | - | - | + | Acute hepatitis C |

**58. Answer is A (IgM - Anti - HBc antibody) :** *Harrison 16th / 1833, 1832; Harrison 17th/ 1943 Harrison 18th/p 2550*

***If IgM - Anti - HBc is present the Hepatitis B infection is considered acute*** - *Harrison 16th / 183*

**<u>The presence of Hepatitis B virus infection is represented by the presence of HBs Ag and IgM Anti - HBc antibody.</u>**

- If IgM Anti HBc is present the HBV infection is considered acute.
- If IgM Anti HBc is absent the HBV infection is considered chronic.

| HBs Ag | IgM Anti - HBc | Diagnostic interpretation |
|---|---|---|
| + | + | Acute Hepatitis B |
| + | - | Chronic Hepatitis B |
| - | + | Acute Hepatitis B (HBs Ag below detection threshhold) |

- The presence of **HBeAg** only denotes High infectivity and active disease.
  HBeAg may be present in both Acute and Chronic Hepatitis B infection.

- **HBV DNA** like HBe Ag is an indicator of HBV replication - *Harrison 16th*
  The presence of HBV DNA therefore also represents an indicator for infectivity and active disease and may be seen both in acute and chronic Hepatitis B infection.
  HBV DNA detection has high sensitivity and may be detected when HBe Ag is still undetectable.

**59. Answer is B (HBs Ag + HBe Ag):** *Harrison 15th/1731; 16th/1832; 17th/1934 Harrison 18th/p 2550*

***HBe Ag: Its principal clinical usefulness is an indicator of relative infectivity – Harrison***
***HBs Ag:*** *Its presence in serum indicates infection / pervious vaccination with hepatitis B virus.*

| | HBs Ag | Anti- HBsAg | Anti Hbc | HBe Ag | Anti-Hbe |
|---|---|---|---|---|---|
| ***Acute HBV infection High infectivity*** | + | - | IgM | + | - |
| ***Chronic HBV infection High infectivity*** | + | - | IgG | + | - |

*Thus, the presence of the above two markers indicate an infection with hepatitis B virus and high infectivity.* Q
**Whether the infection is acute or chronic can, however, only be commented if status of anti-HBe marker is clear.**

**60. Answer is D (HBs Ag) :** *Harrison 18th/p 2540, 2541 Harrison 17th/1933, 1935; CPDT 16th/662*

***HBsAg is not a marker for active HBV Replication. Serological markers for active viral replication include HBe Ag, presence of DNA polymerase and circulating HBV DNA***

Markers for HBV Replication

| Qualitative Markers | Quantitative Markers |
|---|---|
| ***HBe Ag*** *is a qualitative marker for HBV replication* | • ***HBV DNA*** *is a quantitative definitive marker for HBV replication*<br>• ***DNA polymerase*** *is a definitive marker for HBV replication* |

| Serological markers for Active viral Replication |
|---|
| 1.HBV DNA (Definitive) |
| 2.HBV DNA polymerase (Definitive) |
| 3.HBeAg (Qualitative) |

**61. Answer is D (HBV-DNA estimation):** *Harrison 16th/1832; 17th/ 1933-34, 1943-44; 18th/2540, 2541, 2550, 2551*

*Like Hbe Ag, serum **HBV DNA** is an indicator of HBV replication, but tests for HBV DNA are more sensitive and quantitative - Harrison 16th/1832*
The marker HBV DNA is useful in following the course of HBV replication and thus deciding need for antiviral chemotherapy.

**Interferon therapy** would be started after adjudging its need as indicated by HBV DNA testing.

**Liver biopsy** would be too radical at this stage.

**62. Answer is A (Anti HBsAg positive):** *Harrisons 17th/1943 Harrison 18th/p 2550*

***Presence of Anti HBsAg positive status indicates either immunization with HBs Ag or Hepatitis B in the remote past with complete recovery such patients are considered safe for blood transfusion.***

| HbsAg | Anti-HBs | Anti-HBc | HBeAg | Anti-HBe | Interpretation |
|---|---|---|---|---|---|
| - | + | IgG | - | +/- | Recovery from hepatitis B |
| - | + | - | - | - | 1. Immunization with HbsAg (after vacciniation)<br>2. Hepatitis B in the remote past (?)<br>3. False-positive |

**63. Answer is C (Hbs Ag+ and IgM anti-HBc+):** *Harrison 14th/ 1688; Harrison 15th/ 1731; Harrison 16th/1832; Harrison 17th/ 1933, 1934, 1943 Harrison 18th/p 2540, 2541, 2550*

***Presence of 'HBsAg +ve' status along with an IgM type of anti HBc is indicative of acute viral hepatitis B. Such a patient is certainly not considered safe for transfusion.***

- ***Anti HbsAg +ve alone*** : Indicate either
  1. Immunization with HBsAg
  2. Remote past infection
  3. False positive

  Such a patient is considered safe.
- ***Hbc'Ag' is never detectable in the serum***, and this is a false proposition altogether.
- **Anti Hbe +ve** alone is insufficient data to comment up on. However presence of anti Hbe Ag. indicates HBV infection with low infectivity. *Although transfusion is not advisable in this case, this person is safer than option (c).*

**64. Answer is C ('P' gene):** *Harrison's 14th/ 1679; 15th/1722; 16th/1823; 17th/ 1933 Harrison 18th/p 2538, 2539, 2540*

***The reverse transcriptase activity is a property of DNA polymerase which is coded by 'P' gene.***

**Genomic structure of Hepatitis B:**

| 'S' Gene | 'C' Gene | 'P' Gene | 'X' Gene |
|---|---|---|---|
| Codes for the envelope protein, Hbs Ag. | Codes for two nucleocapsid protein.<br>a. Hbc Ag: The intracellular core protein.<br>b. Hbe Ag: A soluble non particulate nucleocapsid protein. | Codes for DNA polymerase<br>This DNA polymerase has two acitivities:<br>a. DNA dependent DNA Polymerase<br>b. ***RNA dependent Reverse Transcriptase.*** | Codes for Hbx Ag.<br>It is a small non particulate protein, that can transactivate the transcription of cellular and viral gene. |

**65. Answer is D (Serial Monitoring) :** *Harrison 18th/p 2569-2577 Harrisons 17th/1957- 1962*

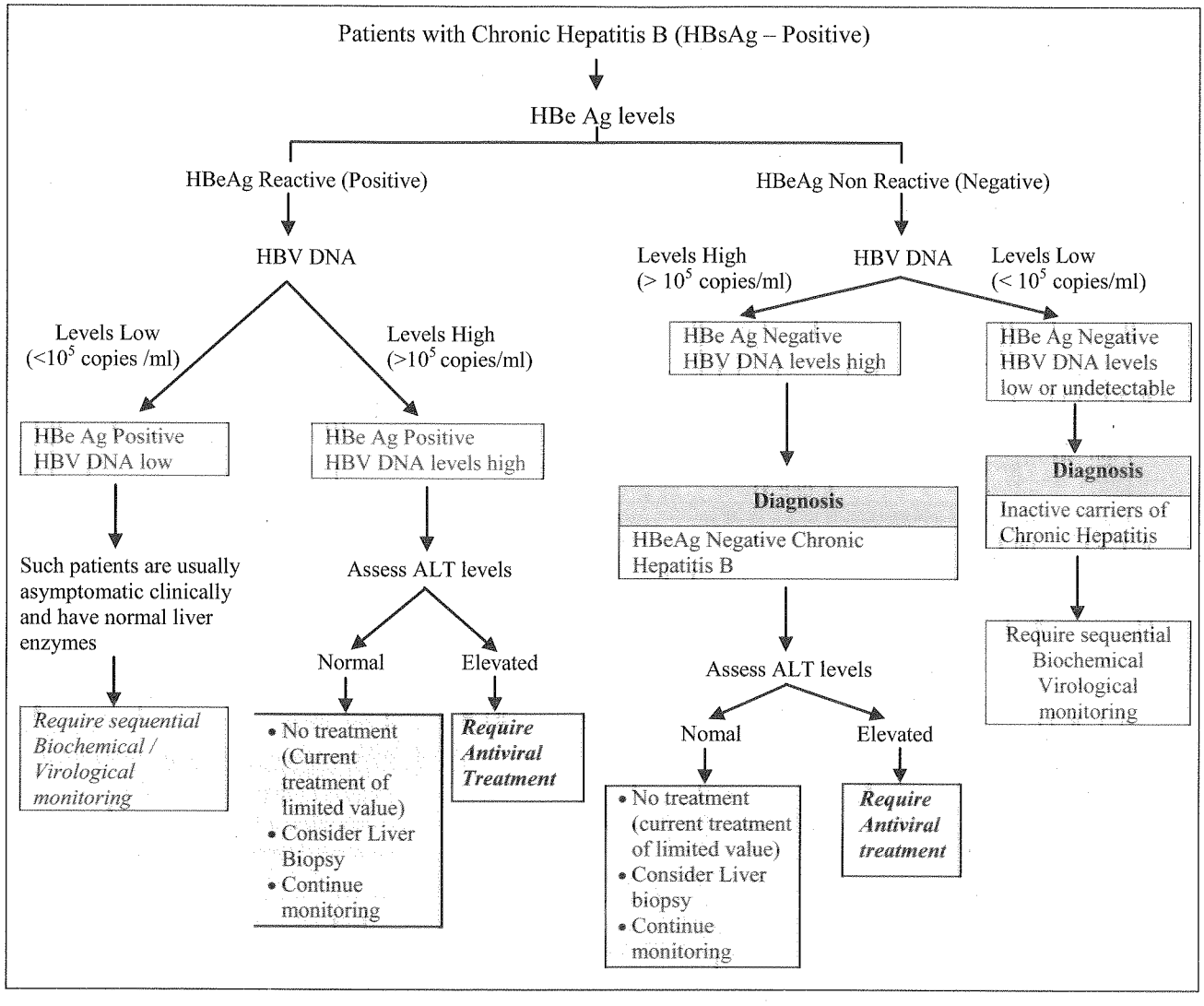
*Antiviral therapy (IFN, Lamuvidene, Adefovir, Entecovir) for chronic hepatitis B is indicated for patients with active HBV replication. Negative HBe Ag and Normal levels of liver enzymes suggest that the patient is either in a* ***non replicative phase of chronic hepatitis****, or, is an inactive carrier of chronic Hepatitis.*

***Such patients are best managed by sequential monitoring (biochemical and virological) over many months and are not considered candidates for antiviral therapy***

**Assessment of need for Antiviral therapy in Chronic Hepatitis B**

*Antiviral therapy is indicated for patients with active HBV replication*
*Active HBV replication is best assessed by measuring serum HBe Ag levels and HBV DNA levels*

| Markers for Active HBV Replication |
|---|
| *HBe Ag*$^{Q}$ |
| *HBV – DNA*$^{Q}$ |




***The patient in question is negative for HbeAg and has normal ALT levels. He is thus not a candidate for antiretroviral therapy. Such patients are best managed by sequential monitoring (biochemical and virological) over many months.***

**66. Answer is A (Serial monitoring):** *Harrison's 18th/2576*

***HBe Ag Negative individuals with ALT ≤ upper limit of normal do not require anti-viral treatment. Such individuals may be monitored sequentially with biochemical or virological markers.***

***The patient in question is negative for HbeAg and has normal ALT levels. He is thus not a candidate for antiretroviral therapy. Such patients are best managed by sequential monitoring (biochemical and virological) over many months.***

Seven drugs have been approved for treatment of chronic Hepatitis B (Harrisons)

1. *Interferon α (and Pegylated Interferon)*
2. *Lamuvudine (oral)*
3. *Adefovir (oral)*
4. *Entecavir (oral)*
5. *Dipivoxil (oral)*
6. *Telbivudine*
7. *Tenofavir*

**Recommendations for Treatment of Chronic Hepatitis B**

Based on practice guidelines of the American Association for the Study of Liver Diseases (AASLD).

| HBeAg status | Clinical | HBV DNA (IU/ml) | ALT | Recommendation |
|---|---|---|---|---|
| HBeAg-reactive | Mild or Inactive Liver disease | >2 x$10^4$ | ≤ 2 x ULN | No treatment; monitor. In patients >40, with family history of hepatocellular carcinoma, and/or ALT persistently at the high end of the twofold range, liver biopsy may help in decision to treat |
| | Chronic hepatitis | >2 x $10^4$ | >2 x ULN | Treat[e] |
| | Cirrhosis compensated | >2 x $10^3$ | < or > ULN | Treat[e] with oral agents, not PEG IFN |
| | | <2 x $10^3$ | >ULN | Consider treatment |
| | Cirrhosis decompensated | Detectable | < or > ULN | Treat[e] with oral agents[g], not PEG IFN; refer for liver transplantation |
| | | Undetectable | < or > ULN | Observe; refer for liver transplantation |
| HBeAg-negative | Mild or Inactive Liver disease | ≤ 2 x $10^3$ | ≤ULN | Inactive carrier; treatment not necessary |
| | Chronic hepatitis | >$10^3$ | 1->2 x ULN | Consider liver biopsy; treat[h] if biopsy shows moderate to severe inflammation or fibrosis |
| | Chronic hepatitis | >$10^4$ | >2 x ULN | Treat[h,i] |
| | Cirrhosis compensated | >2 x $10^3$ | < or > ULN | Treat[e] with oral agents, not PEG IFN |
| | | <2 x $10^3$ | >ULN | Consider treatment |
| | Cirrhosis decompensated | Detectable | < or > ULN | Treat[h] with oral agents[g], not PEG IFN; refer for liver transplantation |
| | | Undetectable | < or > ULN | Observe; refer for liver transplantation |

[e] One of the potent oral drugs with a high barrier to resistance (entecavir or tenofovir) or PEG IFN can be used as first-line therapy. These oral agents, but not PEG IFN, should be used for interferon-refractory/intolerant and immunocompromised patients. PEG IFN is administered weekly by subcutaneous injection for a year; the oral agents are administered daily for at least a year and continued indefinitely or until at least 6 months after HBeAg seroconversion.

[g] Because the emergence of resistance can lead to loss of antiviral benefit and further deterioration in decompensated cirrhosis, a low-resistance regimen is recommended-entecavir or tenofovir monotherapy or combination therapy with the more resistance-prone lamivudine (or telbivudine) plus adefovir. Therapy should be instituted urgently.

[h] Because HBeAg seroconversion is not an option, the goal of therapy is to suppress HBV DNA and maintain a normal ALT. PEG IFN is administered by subcutaneous injection weekly for a year; caution is warranted in relying on a 6-month posttreatment interval to define a sustained response, because the majority of such responses are lost thereafter. Oral agents, entecavir or tenofovir, are administered daily, usually indefinitely or, until as very rarely occurs, virologic and biochemical responses are accompanied by HBsAg seroconversion.

[i] For older patients and those with advanced fibrosis, consider lowering the HBV DNA threshold to >2 x $10^3$ IU/ml.

***Abbreviations***: ULN, upper limits of normal; PEG IFN, pegylated interferon.

**67. Answer is C (ALT > 2x ULN):** *Harrison's 18th/2576*

***The primary indication of antiviral treatment in chronic hepatitis B is elevation of ALT levels to more than 2 times the upper limit of normal.***

*Antiviral treatment is recommended for treatment of chronic hepatic B in both HBe Ag positive and HBe Ag negative individuals when HBV DNA > 2 x $10^4$ U/ml and ALT > 2 times ULN.*
*Lamivudine is the first of the nucleoside analogues to be approved and may be used for Antiviral treatment in such cases although newer, more potent agents are now generally preferred.*

**68. Answer is B (Acute Viral Hepatitis B - Antiviral therapy):** *Harrison 18th/p 2554 Harrison's 17th/1946, 1956: 'Clinical Hepatology: Principles & Practice of Hepatobiliary Disease' (Springer, 2010) /761*

***Acute Viral Hepatitis B is not an indication of Antiviral therapy. Antiviral therapy is not indicated for Acute Hepatitis B.***

**Acute Hepatitis B is not an approved indication for Antiviral Therapy**

In the vast majority of patients Acute Hepatitis B is a self limiting disease that results in viral elimination and complete healing.

*'In Hepatitis B among previously healthy adults who present with clinically apparent hepatitis, recovery occurs in ~ 99%; therefore antiviral therapy is not likely to improve the rate of recovery and is not required'- Harrison's 17th/1946*

*'The administration of Antiviral therapy (lamivudine) to patients with acute hepatitis B may slow the development of protective Anti- HBs titres. Therefore antiviral treatment is not recommended in patients with uncomplicated acute viral hepatitis B' - Clinical Hepatology (Springer, 2010) /761*

**Note** *(Harrison's 17th/1946; Clinical Hepatology (2010)/761)*

*Antiviral therapy with nucleos(t)ide analogs might be considered for fewer than 1% of patients with acute viral hepatitis B who present with a fulminant clinical course. Although* ***at present severe/fulminant acute hepatitis B is not an approved indication of antiviral therapy*** *and there is no data to support such an approach most authorities would recommended institution of antiviral therapy for severe acute Hepatitis B*

**69. Answer is A (Vertical Transmission is more common than horizontal transmission in non-endemic areas):** *Harrison 18th/p 2547 Harrison's 17th/Park 20th/186, 187*

*Vertical transmission is more common that horizontal transmission in endemic Areas (not in non-endemic areas)*

**Age of onset determines prognosis**

*'The outcome of HBV infection is age dependent. The development of chronic hepatitis B is inversely related to age and occurs in approximately 95% of persons infected perinatally, in 80% of persons infected in early childhood and in 5-10% infected after 5 years of age' – Park 20th/188*

**Period of communicability lasts several months**

*'The period of communicability is usually several months. The virus is present in the blood during the incubation period (for a month before jaundice) and acute phase of disease' – Park 20th/187*

**Virus can be detected in blood one month before jaundice**

*'Circulating HBsAg precedes elevation of aminotransferases and clinical symptoms (jaundice) by 2-6 weeks and remains detectable during the entire icteric or symptomatic phase of acute 'Hepatitis B' and beyond'*
*– Harrison's 17th/1933*

**Vertical transmission is more common in Endemic areas**

*'Perinatal transmission (vertical) is uncommon in North America and Europe (Non-Endemic areas) but occurs with great frequency and is the most common mode of HBV perpetuation in the Far East and developing countries (Endemic areas)' – Harrison's 17th/1940,1947*

**70. Answer is D (Gall stone disease):** *Harrison 18th/p 2547 Hepatology: Principles and Practice 2nd/431 Liver Immunology: Principles and Practice (2007) / 210*

*Gallstone disease has not been mentioned in the list for extrahepatic manifestations of Hepatitis B*

**Extrahepatic manifestations in viral hepatitis B:**

- *Aplastic Anemia*
- *Cryoglobulinaemia*
- *Diabetes mellitus*
- *Dermatomyositis-like syndrome*
- *Gianotti- Crosti syndrome*
- *Glomerulonephritis*

- *Guillain- Barre syndrome*
- *Myasthenia gravis*
- *Pericarditis and myocarditis*
- *Pancreatitis*
- *Peripheral Neuropathy*
- *Polyarleritis Nodosa*
- *Polyarthritis*
- *Polymyalgia rheumatica*
- *Polymyositis*
- *Porphyria cutanea tarda*
- *Psychosis*
- *Raynaud's syndrome*
- *Serum sickness like illness*
- *Splenomegaly and lymph node enlargement*
- *Skin alterations*
- *Thrombopenic purpura*
- *Thyroiditis*
- *Urticaria*



**71. Answer is D (Focal Segmental Glomerulosclerosis) :** *Harrisons 17th/ 1796 ; Liver Immunology; Principles & Practice (2007) / 211 'Viral Hepatitis' be vilson (1997) / 332*

***Focal Segmental Glomerulosclerosis (FSGS) has not been mentioned in association with hepatitis B associated Glomerulonephritis***

*Glomerulonephritis associated with Hepatisis B include, MGN, MPGN and Mesangiocapillary GN*

| Glomerulonephritis during chronic Hepatitis B infection |
|---|
| *Membranous Glomerulonephritis (MGN)* |
| *Membranoproliferative Glomerulonephritis (MPGN)* |
| *Mesanglocapillary glomerulonephritis* |

**Note**

*MGN is most commonly seen **in children**[Q]*
*MPGN is most commonly seen **in adults**[Q]*

**72. Answer is B (↑ HBV DNA and ↑ ALT) :** *Harrison 18th/p 2583 Harrison 17th/ 1961*

***Antiviral therapy with interferon is indicated in patients with active viral replication (↑ HBV DNA) and elevated ALT levels***

*Patient with active DNA replication (↑ HBV DNA) and cirrhosis (compensated or decompensated) should not be treated with Interferon therapy These patients should be treated with other oral agents and IFN*

| Indications for Interferon Therapy |
|---|
| *Chronic Hepatitis with ↑ HBV DNA and Elevated LFT* |

**73. Answer is E (Famcyclovir):** *Harrison 18th/p 2569 Harrisons 17th/ 1957*

***Famcyclovir is not an approved drug for treatment of chronic hepatitis B***

| Seven drugs have been approved for treatment of chronic Hepatitis B (Harrisons) |
|---|
| 1. *Interferon alpha and Pegylated Interferon (PEG)* |
| 2. *Lamuvudine (oral)* |
| 3. *Adefovir (oral)* |
| 4. *Entecavir (oral)* |
| 5. *Dipivoxil (oral)* |
| 6. *Telbivudine* |
| 7. *Tenofovir* |

**74. Answer is A (Entecavir):** *Harrsion 18th; Harrison's Infectious Diseases 2nd/ 982*

*Entecevir is the first line drug of choice for Hepatitis B.*

*'Its high barrier to resistance coupled with its high potency renders **entecavir** a first-line **drug** for patients with chronic **Hepatitis B**' - Harrison*

**75. Answer is B (Diabetics on Insulin):** *Harrison 18th/ 1035*

*Diabetic Patients on Insulin are not classified as High Risk Individuals that require Hepatitis B Vaccination.*

| Indication for Hepatitis B Vaccination in Adults |
|---|
| • **Behavioral:** Sexually active persons who are not in a long-term, mutually monogamous relationship (e.g., persons with more than one sex partner during the previous 5 months): persons seeking evaluation or treatment for a sexually transmitted disease (STD): current or recent injection-drug users; and men who have sex with men.<br>• **Occupational:** Healthcare personnel and public-safety workers who are exposed to blood or other potentially infectious body fluids.<br>• **Medical:** Persons with end-stage renal disease, including patients receiving hemodialysis; person with HIV infection; and persons with chronic liver disease.<br>• **Other:** Household contacts and sex partners of persons with chronic HBV infection; clients and staff members of institutions for persons with developmental disabilities; and international travellers to countries with high or intermediate prevalence of chronic HBV infection. |

**76. Answer is C (Intra-muscular deltoid)**

***The preferred site for hepatitis B vaccination is intramuscular into the deltoid.*** *Injection into the buttock/Gluteal region has been associated with decreased immunogenicity of hepatitis B presumably because of inadvertent subcutaneous injection or injection into deep fat tissue. The fat in the buttock reduces the immunogenicity of the vaccine.*

## Hepatitis C

**77. Answer is C (Hepatitis C):** *Harrison 18th/p 2546 Harrison's 17th/1939; Harrison's 16th/1829; Refer previous question*

*Most common hepatitis to progress to chronicity is hepatitis C*

| Parameter | HAV | HBV | HCV | HDV | HEV |
|---|---|---|---|---|---|
| Progression to chronicity | None | Occasional (1-10%) | Common (50-70%) | *Common | None |

** In acute HBV/HDV co infection, the frequency of chronicity is the same as that for HBV. In HDV superinfection chronicity is variable*

**Clinical and epidemiologic features of viral hepatitis:**

| Features | HAV | HBV | HCV | HDV | HEV |
|---|---|---|---|---|---|
| **Incubation (days)** | 15-45 | 30-180 | 15-160 | 30-180 | 14-60 |
| **Age** | Children, young Adults | Young adults | Any age but more in adult | Any age | Young adults |
| **Transmission** | | | | | |
| *Fecal-oral* | +++ | --- | --- | --- | +++ |
| *Percutaneous* | Unusual | +++ | +++ | +++ | --- |
| *Perinatal* | --- | +++ | + | + | --- |
| *Sexual* | + | ++ | + | ++ | --- |
| **Clinical** | | | | | |
| *Severity* | Mild | Occasionally Severe | Moderate | Occasionally Severe | Mild |
| *Fulminant* | .1% | .1%-1% | .1% | 5-20% | 1-2% |
| *Progression to chronicity* | None | Occasional (1-10%) | Common (50-70%) | Common | None |
| *Carrier* | None ♀ | 01%-30% | 1.5 to 3.2% | Variable | None ♀ |
| *Cancer* | None ♀ | +nt | +nt | Variable | None ♀ |
| *Prognosis* | Excellent | Worse with age | Moderate | Acute: good Chronic: poor | Good |
| *Prophylaxis* | IgG Vaccine | HBIG Recombinant vaccine | None | - | Unknown |

**Memo :** ♀ *HCV is the most common Virus associated with transfusion associated hepatitis*
♀ *No vaccine / prophylaxis is available for HCV*
♀ *Malignant potential is present with HCV (also with HBV)*

**78. Answer is A (Anti-LKM antibody):** *Harrison 14th/ 1687, 1703; 15th/ 1751, 1747; 16th / 1828; 17th/ 1942; 18th/2550*

***Hepatitis C is associated with Anti-LKM antibodies.*** *Hepatitis C may possibly also be associated with cryoglobulinemia but in view of its definite association with anti-LKM antibodies, this is the single best answer.*

**LKM antibodies** stand for antibodies against Liver-Kidney microsomes.

| LKM antibodies may be seen in |
|---|
| - Type II autoimmune hepatitis (anti LKM-I) |
| - Drug induced hepatitis (anti LKM-II) |
| - Chronic hepatitis C |
| - Chronic hepatitis D (anti LKM-III) |

*Note that species of LKM antibodies in hepatitis C and hepatitis D are different from each other as well as from LKM antibodies in autoimmune hepatitis type II.*

- *Hepatitis C is also associated with* ***essential mixed cryoglobulinemia (EMC)*** *- Harrison 14th/1683*
  Essential mixed cryoglobulinemia is an extrahepatic manifestation of viral hepatitis. It was reported initially to be associated with hepatitis B. Recent reevaluation of patients with EMC suggests that association is with chronic HCV infection rather than HBV infection.
- ***PAN*** *is associated with hepatitis B virus and not with hepatitis C.*
- ***Scleroderma*** *is not associated with Hepatitis C.*

**79. Answer is B (Celiac disease):** *'Hepatology: Principles and Practice' by Kuntz 2nd/443*

***Celiac disease has not been mentioned in list of extrahepatic manifestations of hepatitis C***

**Extrahepatic manifestations in viral hepatitis C:** *'Hepatology' by Kuntz*

- *Agranulocytosis*
- *Aplastic anaemia*
- *Corneal ulceration*
- *Cryoglobulinaemia*
- *Diabetes mellitus (type I)*
- *Erythema exsudativum multiforme*
- *Glomerulonephritis*
- *Guillain-Barre syndrome*
- *Hyperlipasaemia*
- *Lichen planus*
- *Non-Hodgkin lymphoma*
- *Polyarteritis nodosa*
- *Polyarthritis*
- *Polyneuritis*
- *Porphyria cutanea tarda*
- *Sialadenitis*
- *Sjogren's syndrome /Sicca syndrome*
- *Thrombocytopenia*
- *Thyroiditis*

**80. Answer is B and D (Dermatomyositis like syndrome> Psoriasis):** *'Dermatology byBurg dorf (Thieme Clinical companion Series) 2006/66*

***Dermatamyositis like syndrome has not been mentioned in association with Hepatitis C infection.***

***Psoriasis has also not been linked to Hepatitis C virus directly although it may be seen in patients treated with Interferon α***

*Lichen planus and PAN are established associations of both, hepatitis B and hepatitis C.*

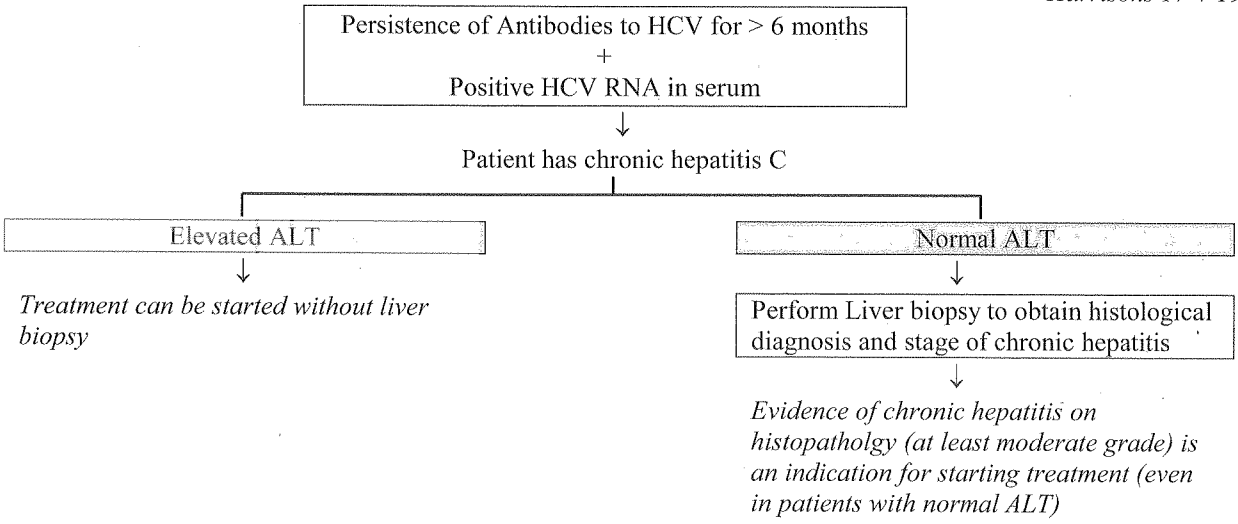
| Dermatoscs associated with Hepatitis B | Dermatoses associated with Hepatitis C |
|---|---|
| • Gianotti-Crosti syndrome<br>• Lichen planus<br>• Mixed cryoglobulinemia<br>• Erythema nodosum<br>• Pyoderma gangrenosum<br>• Polyarteritis nodosa<br>• Urticaria<br>• Leukocytoclastic vasculitis<br>• Serum sickness-like prodrometeinuria, or hematuria<br>• Dermatomyositis-like syndrome | • B-cell lymphoma (lymphoplasmacytic lymphoma, Waldenstrom macroglobulinemia) associated with mixed cryoglobulinemia.<br>• Leukocytoclastic vasculitis<br>• Polyarteritis nodosa<br>• Porphyria cutanea tarda<br>• Lichen planus<br>• Urticaria |

*Many dermatoses formerly associated with HBV infection have turned out to be more often or exclusively associated with HCV. Thus, both of these lists should be viewed as working formulations.

**81. Answer is D (Do liver biopsy and start antiviral treatment accordingly):** *Harrison 18th/p 2582 Harrisons 17th/ 1965*

*Antibodies against HCV (anti- HCV) in the blood indicate infection with the HCV. Persistance of antibodies for 6 months suggests a diagnosis of chronic hepatitis C. Patients with chronic hepatitis C, even with normal ALT levels are candidates for Liver biopsy to establish a histo-pathological diagnosis of chronic hepatitis.* ***Patients with at least moderate grade and stage are candidates for antiviral therapy with PEG IFN and ribararin regardless of the ALT levels***

*'Although patients with persistantly normal ALT levels tend not to progress histologically, they respond to antiviral therapy just as well as do patients with elevated ALT levels. Such patients are potential candidates for antiviral therapy'*
*- Harrisons 17th/ 1965*



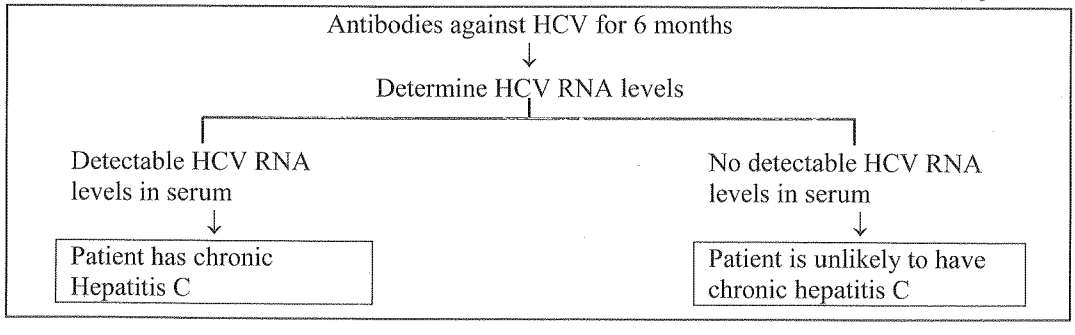

Chronic hepatitis : 'Evidence Based medicine Guidelines' 1st (2005) / 330

- Increased serum ALT 6 months after the onset of symptoms: (normal ALT does not, however, rule out chronic hepatitis).
- A patient with a positive HCV-PCR-test and permanently elevated ALT most probably has a mild chronic hepatitis and treatment decisions can be made without liver biopsy in genotypes 2 and 3.
- Liver biopsy is indicated in a patient with positive HCV-PCR- test and normal ALT, and with genotypes 1 and 4 before considering therapy. Signs of chronic hepatitis in the biopsy are an indication for treatment.
- Information on the genotype of the virus is important to guide treatment decisions. Treatment is more effective for genotypes 2 or 3 than for genotypes 1 and 4.
- Treatment with a combination of interferon alpha or pegylated interferon alpha and ribavirin is used for 48 weeks for genotypes 1 and 4 and for 24 weeks for genotypes 2 and 3.
- When treating genotypes 1 or 4. If there is no response at 12 weeks (HCV-PCR still positive), the treatment is discontinued.
- Liver transplantation is indicated if the expected survival is about 6 months

**82. Answer is E (Determine HCV RNA levels)**

*Antibodies against HCV in the blood indicate infection with Hepatitis C virus. If the infection persists for more than 6 months and viral replication is confirmed by HCV RNA levels, then the person can be confirmed as having chronic hepatitis C.*

***The next step in the management of the patient in question would be to establish a serological diagnosis of chronic hepatitis (which can be determined by HCV RNA levels in the setting of elevated antibodies to HCV for 6 months).***



*Once a diagnosis of chronic hepatitis C is suggested by the presence of HCV RNA, levels of ALT should be determined to plan appropriate treatment as indicated in the previous question.*

**83. Answer is A (Ribavarin and interferon):** *Harrison 18th/p 2583 Harrison's 17th/1965; Harrison's 16th/1852*

***The patient in question is a relapser after previous standard interferon monotherapy.***
***The recommended treatment of choice for such patients is a course of Interferon plus Ribavarin.***
*'A course of Interferon plus Ribavarin is the recommended treatment of choice for Relapsers after a previous course of standard monotherapy with interferon or combination interferon/ribavarin therapy'- Harrison's*

**Treatment of choice in Hepatitis C infection**

| Recommended treatment for hepatitis C | Recommended Retreatment for Relapsers or Non Responders |
|---|---|
| First line Treatment | First line treatment |
| Combination therapy with PEG – Interferon plus Ribavarin<br>48 weeks of therapy for Genotypes I and 4<br>24 weeks of therapy for Genotypes 2 and 3 | Combination therapy with PEG – Interferon plus Ribavarin |

**84. Answer is A (Ribavarin and interferon):** *Harrison 15th/ 1749, Table 297-6; Harrison 16th/ 1852, 1851; Harrison 17th/ 1965 Harrison 18th/p 2582, 2583*

***'Patients who have relapsed after a course of interferon monotherapy are candidates for retreatment with combination regulated interferon plus ribavarin therapy.'*** *– Harrison 16th/ 1852*

**Indication Of Therapy:**

1. Elevated ALT
2. Portal bridging fibrosis or moderate to severe hepatitis on liver biopsy
3. Detectable HCV RNA

**Treatment options / Regimens:**

| First line treatment (treatment of choice) | Alternate regimen (if ribavarin is C/I) |
|---|---|
| *Combination pegylated IFN plus ribavarin* | *Pegylated interferon monotherapy* |

*Pegylated IFN are long acting IFN's bound to polyethylene glycol. Such pegylated IFN have a substantially longer half life, achieve prolonged concentration, permitting administration once a week.*

**85. Answer is E (Female sex):** *Harrison 18th/p 2583 Harrisons 17th/1965 Hand book of Gastroenterology 1st / 129*

***Female sex is a favourable feature, associated with sustained responsiveness to antiviral therapy Male sex is associated with reduced responsiveness.***

| Reduced Responsiveness | Sustained Responsiveness |
|---|---|
| • ***Genotype 1*** | • Genotype 2 and 3 |
| • High levels of HCV RNA | • Low levels of HCV RNA |
| • ***Adranced fibrosis (ciorrhosis, bridging fibrosis)*** | • Minimal fibrosis |
| • Long duration disease | • Short duration disease |
| • ***Age > 40 years*** | • Age < 40 years |
| • Immunosupression | • Immunocompetance |
| • African American | Others |
| • Obesity | • Absence of obesity |
| • Hepatic steatosis | • Absence of Hepatic steatosis |
| • Reduced adherence | • Increased Adherence |
| • Male sex (*Handbook of Gastroenterology*) | • Female sex (*Handbook of Gastroenterology*) |

## Hepatitis E

**86. Answer is B and D (Associated with increased mortality in pregnant women and Acquired by Fecooral route):** *Ananthnarayanan 6th/519; Park 18th/174l; Harrison's 17th/1934, 41, 44; Harrison's 18th/1829, 1831, 1834 Harrison 18th/p 2538, 2548, 2552*

***Hepatitis E is associated with increased mortality in pregnant women and is acquired by fecooral route.***
*Hepatitis E is not associated with transfusion with Hepatitis B virus infection.*

**Hepatitis E is transmitted by fecooral route and not transmitted by transfusion**

| Transmission Q | HAV Q | HBV Q | HCV Q | HDV Q | HEV Q |
|---|---|---|---|---|---|
| Fecooral | +++ | - | - | - | +++ |
| Percutaneous | Unusual | +++ | +++ | +++ | - |
| Perinatal | - | +++ | ± | + | - |
| Sexual | ± | ++ | ± | ++ | - |

Q *Most common virus associated with transfusion associated hepatitis is HCV.*

**Hepatitis E is associated with increased mortality in pregnant females**

*A unique feature of Hepatitis E virus is the clinical severity and high case fatality rate of 20-40% in pregnant women, especially in the last trimester of pregnancy.*

**Hepatitis D is associated with Hepatitis B infection and not Hepatitis E**

**87. Answer is B (Feco-oral):** *Park 17th/ 165; Harrison 16th / 1829±, 1831; 17th/ 1939, 1941 Harrison 18th/p 2538, 2548*

*Hepatitis E is synonymous with Enterically transmitted non-A non-B Hepatitis.*
***The infection caused by hepatitis E is essentially a water borne disease- Water or Food supplies, contaminated with feces in which the virus is excreted, have been implicated in major outbreaks reported in all parts of the world.***

| Transmission Q | HAV Q | HBV Q | HCV Q | HDV Q | HEV Q |
|---|---|---|---|---|---|
| Fecooral | +++ | - | - | - | +++ |
| Percutaneous | Unusual | +++ | +++ | +++ | - |
| Perinatal | - | +++ | ± | + | - |
| Sexual | ± | ++ | ± | ++ | - |

Q *Most common virus associated with transfusion associated hepatitis is HCV.*

**88. Answer is A (Pregnant women):** *Ananth Narayan 6th/ 519; Park 18th /174; 17th/ 1944-45 Harrison 18th/p 2552, 2553*

***A unique feature of Hepatitis E virus is the clinical severity and high case fatality rate of 20-40% in pregnant women, especially in the last trimester of pregnancy.***

**89. Answer is A (Pregnant women):** *Harrison 17th /1939, 1941; Harrison's 18th/174; Robbins 7th/891;De swiet's Medical Disorders in Obstetric Practice (John Wiley & Sons) 2010/230*

***Fulminant Hepatitis E is typically seen in pregnant women especially in the last trimester.***

*'A unique feature of Hepatitis E virus is the clinical severity and high case fatality rate (20-40%) in pregnant women, especially in the last trimester of pregnancy'. - Park*

*'Hepatitis E can lead to fulminant hepatitis which happens most frequently amongst pregnant women than any other subgroup' – De Swiet's Medical Disorder in Obstetric Practice.*

**90. Answer is D (Hepatitis E):** *See previous question; Harrison 18th/p 2552, 2553 Harrison 17th/ 1944-45*

**91. Answer is C (HEV):** *See previous question; Harrison 18th/p 2552, 2553 Harrison 17th/ 1944-45*

**92. Answer is D (Hepatitis E):** *Park 18th/174; Harrison 18th/2538, 2548; 17th/1939, 1941, Park 17th/165, Ananth Narayan 7th/559*

***Epidemics are almost exclusively caused by enterically transmitted NON A NON B Hepatitis virus - i.e. Hepatitis E.*** Q
*- Park*

*Sporadic cases* :
Most common cause of ***sporadic cases in adults is - Hepatitis E*** Q
Most common cause of ***sporadic cases in children is - Hepatitis A.*** Q

**93. Answer is A (Hepatitis E) :** *Zokin & Boyer's Hepatology: A textbook of Liver Diseases (Elsvier)2011/612; Schiff's Diseases of the Liver (John Willey & Sons)2011/chapter 23*

***The most common cause of acute sporadic hepatitis amongst adults in India is Hepatitis E.***

*'In India HEV infection is the most common cause of acute sporadic hepatitis and account s for upto 70% of such cases amongst adults' - Zokin & Boyer's Hepatology*

*'Hepatitis E is the second leading cause of acute clinical hepatitis in adults in North African and the middle east (after Hepatitis B) and is the most common cause in Nepal, India and throughout central & south east Asia.*
*- Schiff - Diseases of the Liver*

*'Hepatitis E is the most common cause of a sporadic and epidemic Hepatitis amongst adults in Asia (India) and the second most common cause amongst adults (after HBV) in the middle east and north Africa'*
*- De Sweet's Medical Disorder in Obstetric Practice*

| Hepatitis E (HEV) |
|---|
| • *Most common cause of sporadic Hepatitis amongst adults in India*$^{Q}$ |
| • *Most common cause of epidemic Hepatitis amongst adults in India*$^{Q}$ |
| • *Most common cause of Fulminant Hepatitis amongst pregnanat women*$^{Q}$ |
| • *Most common route of aquisition /transmission is fecoral route*$^{Q}$ |

## Autoimmune and Granulomatous Hepatitis

**94. Answer is D (ANCA):** *Harrison 18th/2586; Harrisons 17th/1967 Oxford Textbook of Medicine 4th/ 722*

***The characteristic autoantibodies in autoimmune hepatitis include ANA, Anti SLA and, Anti LKM antibodies and anti SMA antibodies***

***Although p ANCA may be seen in patients with type I autoimmune hepatitis, these antibodies are not considered characteristic for any type of autoimmune hepatitis.***

| Characteristic Autoantibodies for Auto immune Hepatitis |
|---|
| • *Antinuclear Antibodies (ANA)* |
| • *Anti LKM Antibodies (Anti- Liver-kidney microscomal antibodies)* |
| • *Anti- SLA (Antibodies against Soluble Liver Antigens)* |
| • *Anti- SMA (Antibodies against smooth muscle Antigens* |

Autoimmune Hepatitis

| Type I | Type II | Type III |
|---|---|---|
| Characteristic Autoantibody profile | Characteristic Autoantibody Profile | Characteristic Auto antibody profile |
| *ANA ++*<br>*SMA ++* | ***Anti LKM1 ++*** | ***Anti – SLA ++***<br>***ANA +/- ; SMA +/-*** |
| Associated Antibody Profile | Associated Antibody Profile | Associated Antibody profile |
| *P ANCA*<br>*Anti – Actin*<br>*Anti – ASGPR* | *Anti- LC1*<br>*Anti – ASGPR* | *Anti – ASGPR* |

*ANA (Antinuclear Antibodies); anti- ASGPR (antibody to asialoglycoprotein receptor); anti LC1 (antibody to Liver cytosol type I); anti- LKM1 (antibody to soluble liver kidney microsome Type I); anti, SLA (antibody to soluble liver antigen).*

**95. Answer is D (All of the above):** *Harrison 15th/e 1739, 1759; 16th/ 1840, 1872; Harrison 17th 1739, 1759 (17th/ not elaborated)*

| Granulomatous Hepatitis has been implicated with the following drugs: |
|---|
| 1. ***Phenylbutazone*** [Q] |
| 2. *Sulfonamides* [Q] |
| 3. *INH* [Q] |
| 4. ***Allopurinol*** [Q] |
| 5. *Quinidine* [Q] |
| 6. ***Carbamazepine*** [Q] |

## Alcoholic Hepatitis

**96. Answer is C (Elevated serum Albumin):** *Harrison 18th/p 2590, 2530 Harrison's 17th/1970, 1971, 1926,264*

***Alcoholic hepatitis is associated with hypoalbuminemia or decreased serum albumin levels (and not elevated serum albumin).***

*'Severe alcoholic hepatitis is heralded by coagulopathy (prothrombin time>5 sec), hypoalbuminemia (albumin<25g/L or 2.5 g/dl) elevated bilirubin levels (>137μmol/l or > 8mg/dl), anemia, renal failure and ascitis.- Harrison's*

**Feature of Alcoholic Hepatitis**

| Features suggesting Hepatocyte injury (Enzyme studies) | Features suggesting dearrangement in Hepatocyte function |
|---|---|
| **AST/ALT** : Levels are increased<br>: Increased is less than 8 fold (< 400u/L)<br>: AST is elevated greater than ALT<br>: AST: ALT Ratio >1<br>AST: ALT>2 is suggestive<br>AST: ALT>3 is highly suggestive<br><br>**Alkaline Phosphatase**:<br>Levels are increased (may be normal)<br>Increase is moderate (<3 times normal)<br>Normal to < 3 times normal elevation<br><br>**Gamma Glutamyl Transpeptidase (GGT)** : Levels are increased<br>: Note that GGT elevation is not specific to alcohol<br>GGT is easily inducible and may be elevated in all forms of fatty liver | **Bilirubin** : May be markedly elevated<br>Both fractions (direct/indirect) may be elevated<br><br>**Albumin** : Often decreased (Hypoalbuminemia)<br>(Albumin <2.5 mg/dl)<br>suggests severe alcoholic hepatitis<br><br>**Prothrombin time** : Often prolonged<br>Fails to correct with parentral vit K<br>(Coagulopathy)<br><br>Others :<br>*Polymorphonuclear cells (Neutrophils)* are often increased and if > 5500/μl predict severe alcoholic hepatitis.<br>*Hypertriglyceredemia* and *Hypercholesterolemia* may be associated with alcoholic fatty liver. |

**97. Answer is B (Alcoholic Hepatitis):** *Harrison 18th/2529, 2590; 17th/1925,1970,1971; Harrison's 16th/1815, 1855, 1856*

***An AST/ALT ratio of greater than 1 suggests a diagnosis of alcoholic hepatitis***

Pattern of aminotranferases and etiology of hepatitis

| Alcoholic Hepatitis | Non Alcoholic Hepatitis (Viral/toxin induced) |
|---|---|
| • AST/ALT Ratio > 1<br>AST: ALT>2:1 is suggestive<br>AST: ALT>3:1 is highly suggestive<br>• AST/ALT elevation is moderate and rarely >400 u/L<br>• AST is elevated more than ALT<br>*The low level of ALT in alcoholic liver disease is due to an alcohol induced deficiency of pyridoxal Phosphate.* | • AST/ALT ratio <1<br>• AST/ALT elevation is usually more marked and often >500 u/L<br>• ALT is elevated more than AST |

**98. Answer is B (SGPT > SGOT):** *Harrison 15th/ 1713; 1753; 16th/ 1856, 1857, 1815; 17th/ 1925 Harrison 18th/p 2529*

*AST is synonymous with SGOT & ALT is synonymous with SGPT*

*In general AST and ALT levels rise parallel to each other.* ***In alcoholic liver disease the AST rises out of proportion to ALT such that the ratio of AST and ALT may become greater than 2.***

**Stigmata of Alcoholic hepatitis / cirrhosis that aid in diagnosis :**

1. Bilateral enlarged parotids Q
2. Gynaecomastia Q
3. Testicular atrophy with loss of body hair Q
4. Wasting of muscle mass Q
5. Duputyrens contracture Q

| AST (SGOT) out of proportion to ALT (SGPT) seen in Q |
|---|
| 1. Alcoholic hepatitis Q |
| 2. Fatty liver in pregnancy Q |

**Gamma Glutamyl transferase levels** correlate with levels of Alkaline phosphatase and are a sensitive indicater of biliary tract disease – obstructive jaundice. *It is not an indicator of alcoholic liver disease.*
*Remember : GGT is the most sensitive indicator of biliary tract disease*

**99. Answer is A (SGOT):** *Harrison 15th/e 1753; 16th/ 1857, 1515, 1815; 17th/ 1925, 1970, 1971; 18th/p 2529, 2590*

*All the enzymes given in the options are elevated in Alcoholic hepatitis. Although none of the options appear to be appropriate, the best options amongst these should be AST or SGOT.*
***In alcoholic hepatitis, in contrast to other causes of fatty liver, the AST and ALT are usually elevated two to seven fold.*** *In general AST and ALT levels rise parallel to each other. In alcoholic liver disease the AST rises out of proportion to ALT such that the ratio of AST and ALT may become greater than 2. AST (SGOT) is therefore the single best answer.*

**AST/ALT > 2:1 is *suggestive*** of alcoholic liver disease.
**AST/ALT > 3 : 1 is *highly suggestive*** of alcoholic liver disease.

**Laboratory diagnosis of alcoholic fatty liver and alcoholic hepatitis.**

| Test | Comments |
|---|---|
| **AST** | • Increase two to seven fold, less than 400U/L, greater than ALT |
| **ALT** | • Increased two to seven fold, less than 400 U/L |
| **AST/ALT** | • Usually less than 1 |
| **GGTP** | • Not specific to alcohol, easily inducible, elevated in all forms of fatty liver. |
| **Bilirubin** | • May be markedly increased in alcoholic hepatitis despite modest elevation in alkaline phosphatase |
| **PMN** | • If > 5500/mL, predicts severe alcoholic hepatitis when discriminant function > 32 |

*Alkaline phosphatase levels may increase but it is not specific to alcohol liver disease*
*Macrocytosis may be seen. (Raised MCV)*

| Alcoholism is also associated with: |
|---|
| • Hypertriglyceremia |
| • Hypercholesterolemia |
| • Hyperbilirubinemia |
| • Increase in circulating polymorphonuclear leucocytes > 5500/μl. |

**100. Answer is A (Alcoholic hepatitis):** *API Textbook of Medicine 9th/ 853*

***Maddrey discriminant score is used for determining severity of Alcoholic Hepatitis and predict mortality.*** .
*Acute hepatitis (AH) in patients with chronic alcoholic liver disease is associated with high mortality. It is therefore vital to identify patients at greatest risk of mortality who may benefit from aggressive intervention and steroid therapy. The Maddrey's Discriminant Function relies on two factors (prothrombin time and serum bilirubin) and suggests which patients with alcoholic hepatitis (Score > 32) may have a poor prognosis and are likely to benefit from steroid administration*

| *Maddrey discriminant score* |
|---|
| Maddrey's discriminant function test was described by Maddrey in 1978 to predict prognosis in alcoholic hepatitis:<br>• It is calculated by: 4.6 × [prothrombin time: control value (seconds)] + serum bilirubin (mg/mL)<br>• During the episode, a score >32 carries a 50% mortality rare and is an indication for treatment with steroids, whereas >90% of pateints with a score <32 will survive. |

**101. Answer is D (Pancreatic lipase deficiency):** *Zakim and Boyer's Hepatology: A Textbook of Liver Disease 6th/408; Goldman's Cecil Medicine 24th edition*

***Zieve Syndrome is a rare syndrome that occurs in individuals with alcohol abuse (alcoholic hepatitis) and is characterized by hemolytic anemia, hyperlipidemia and jaundice.*** *It is believed to be a complication of severe alcoholic liver disease.*

| **Zieve's Syndrome (Alcoholic Hepatitis)** |
|---|
| • ***Hemolytic Anemia*** |
| • ***Jaundice or increased Bilirubin (from a combination of cholestasis and hemolysis)*** |
| • ***Hyperlipidemia*** |

*Zieve's syndrome occurs following acute alcohol poisoning, producing haemolysis and red-cell damage due to hyperlipidaemia and changes within the red-cell membrane.*

**102. Answer is A (Pentoxyfylline):** *Davidson's 20th/971*

***Pentoxy fylline has shown to reduce mortality from renal failure in alcoholic hepatitis.***

*'In severe alcoholic hepatitis oral pentoxyfylline reduces inpatient mortality, particularly from hepatorenal failure'*
*- Davidson*

## Non Alcoholic Fatty Liver Disease (NAFLD/NASH)

**103. Answer is E (Gall stone disease):** *CMDT 2007 / 683; 09/600; Robbins 7th / 907, 908*

***Gall stone disease has not been mentioned as a cause / association of NASH***

| Causes of Non Alcoholic Fatty Liver Disease (NAFLD) or Non Alcoholic Steato hepatitis (NASH) |
|---|

- *Obesity (present in > 40% cases)*
- *Diabetes mellitus (present in > 20% cases)*
- *Hypertriglyceredemia (>20%)*
- *Endocrinopathies (Cushing's and hypopituitarism, PCOS)*
- *Metabolic disorders (Hyperbetalipoproteinemia)*
- *Obstructive sleep apnea*
- *Starvation and Refeeding syndrome*
- *Total parentral Nutrition*
- *Medications and poisons*
  - *Corticosteroids* - *diltiazem* - *irinotecan* - *Antiretroviral therapy*
  - *Amiodarone* - *tamoxifen* - *oxaliplatin* - *$CCl_4$ & Yellow phosphorus*

**104. Answer is B (Clofibrate provides effective treatment):** *Harrison 18th/2604, 2605; 17th/ 1982 ; Robbins 7th/ 907, 908*

***Clofibrate is a lipid lowering drug that decreases hepatic triglyceride content. Based on this, usefulness of clofibrate has been evaluated in the treatment of NASH, however clofibrate has not been found to be effective in the treatment of NASH.***

**Non Alcoholic fatty Liver Disease (NAFLD) is common in Diabetics**

Commonest **Associations of NAFLD / NASH** *(Robbins)*

- *Obesity*
- *Dyslipidemia*
- *Hyperinsulinemia (Insulin resistance is a charachteristic feature$^{Q}$)*
- *Diabetes*

**NAFLD is believed to be the commonest cause of cryptogenic cirrhosis**

*NAFL is now considered the most common cause of 'cryptogenic cirrhosis' – Robbins 7th/908*

**Spectrum of NAFLD**

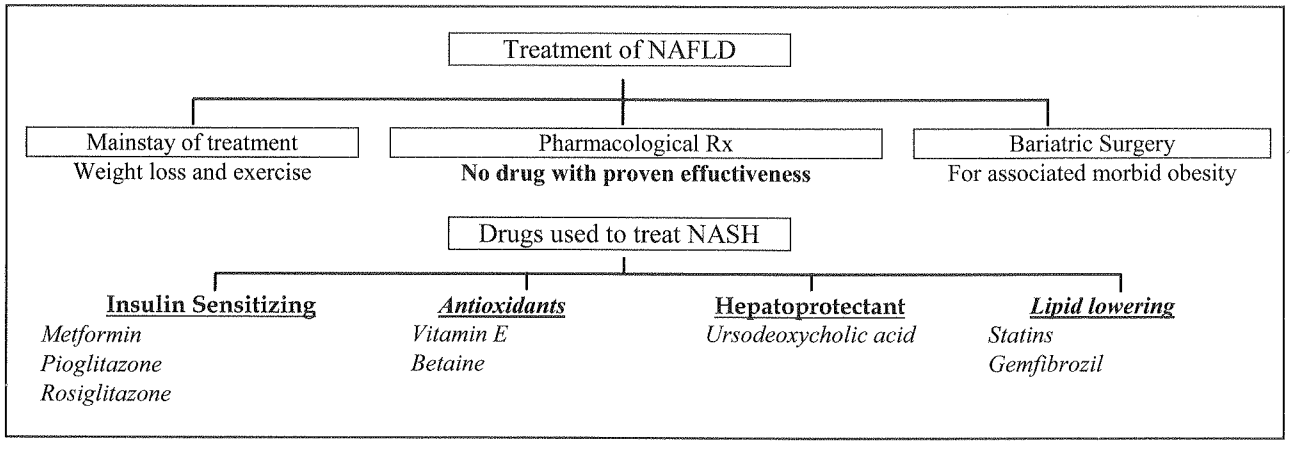
- *Simple steatosis (Early)*
- *Steatohepatitis (NASH) : Non Alcoholic Steatohepatitis) (Intermediate)*
- *Fibrosis and cirrhosis (Advanced)*

**NAFLD is associated with elevated transminases (transaminitis)**

*'Most patients with NAFLD come to medical attention as a result of incidentally elevated liver enzymes' – Harrison*

- ALT > AST
- Aminotransferases are usually only mildly elevated 2 times normal

**Clofibrate has not been found to be effective in the treatment of NAFLD:** *'Fatty Liver Disease:NASH & related disorders' (2005)/ 202*




## Ascitis

**105. Answer is A (Colloid carcinoma of stomach):** *Harrison 15th/ 261; 16th/245; Harrison 17th/268 Harrison 18th/p 332*

*Colloid carcinoma of stomach causes mucinous ascities – Harrisons 16th/ 245*

Chylous Ascitis refers to a turbid milley or crcamy peritoneal fluid due to the presence of thoracic or intestinal lymph. It is most often a result of lymphatic obstruction from the cause mentioned below.

| Causes of Chylous Ascitis | Causes of Mucinous Ascitis |
|---|---|
| Trauma | Pseudomyxoma peritonei |
| Tumor | Colloid carcinoma stomach with peritoneal implants |
| Tuberculosis | |
| Filariasis | Colloid carcinoma colon with peritoneal implants |
| Congenital anomalies | |
| Nephrotic syndrome | |

**106. Answer is D (Pyrrolizidine Alkaloids):** *Textbook of Medical Biochemistry by Chatterjea Shinde (JP) 8th/ 789,790*

*Endemic ascites is caused by pyrrolizidine alkaloids.*

***Endemic ascites*** *is seen in areas where local population subsist on millet Panicum miliare (known locally as Gandhi) which may be adulterated with weed seeds of crotalaria (locally known as Jhunjhunia).On chemical analysis these seeds were found to contain pyrrolizidine alkaloids which are hepatotoxic leading to ascites and jaundice.*

**107. Answer is A (Pyrrolizidine):** *Park 18th /480; Park 19th/525*

*Endemic ascites is caused by pyrrolizidine alkaloids*

***Endemic ascites*** *is seen in areas where local population subsist on millet Panicum miliare (known locally as Gandhi) which may be adulterated with weed seeds of crotalaria (locally known as Jhunjhunia).On chemical analysis these seeds were found to contain pyrrolizidine alkaloids which are hepatotoxic leading to ascites and jaundice.*

**Beta-oxylamino alanine (BOAA) toxin causes Neurolathyrism**

Beta-OxylAmino Alanine (BOAA) toxin is present in seeds of pulse Lathyrus platinum (Khesari daal) causes neurolathyrism.

**Sanguinarine toxin found in Argemone mexicana seeds causes epidemic droopy**

Mustard oil may be adulterated with argemone oil which is derived from wild plant Argemone mexicana. Argemone oil contains the alkaloid, "sanguinarine"' which causes vomiting, diarrhoea and congestive cardiac failure leading to edema. The condition is referred to as epidemic dropsy. Sanguinarine interferes with oxidation of pyruvic acid leading to its accumulation in the blood.

**108. Answer is D (USG can detect as little as 100 ml of peritoneal fluid):** *Current Critical Care Diagnosis & Treatment 3rd/717; Harrisons 17th/267, 268, 1979; Harrison 18th/p 2601, 333 Refer text below*

*Abdominal ultrasound may detect as little as 100 ml of ascitic fluid ultrasound is thus a useful investigation for the diagnosis of minimal ascitis – CCDT 3rd/717*

**Hemorrhagic Ascitis is diagnosed when RBC count >10, 000 / mm$^3$ (Not >1000/mm$^3$)**
*An RBC count of 10,000 / mm$^3$ is the threshold for pink appearance and hemorrhagic ascitis is thus diagnosed when ascitic RBC count is > 10,000 / mm$^3$ - Schiff's diseases of the Liver 10th/ 996*

**Spontaneous Bacterial peritonitis (SBP) is diagnosed when Neutrophil count > 250/mm$^3$**
*The diagnosis of SBP is made when the absolute neutrophil count > 250 / mm3 – Harrisons 17th/1979*

**The drug of choice for treatment of SBP are cephalosporins & not Norfloxacin**
*Cefotaxime is considered the drug of choice for emperic therapy of SBP*

**Large volume Therapeutic Paracentesis is not recommended for SBP**
*Diagnostic paracentesis is indicated in SBP for establishing the diagnosis but large volume paracentesis should be avoided - Schiff's Diseases of the Liver 10th/ 561*

**109. Answer is A (Salt Restriction):** *Harrison 18th/p 2600 Harrisons 17th/ 1978; Oxford Textbook of Medicine 4th/736*

*The first line treatment of Ascitis is dietary salt restriction.*

Treatment of Ascitis: Oxford Textbook of Medicine : Recommendations

- ***Bed Rest*** *is of little value*
- ***Dietry sodium Restriction*** *is the first line management*
- ***Diuretic therapy*** *is the mainstay of treatment of Ascitis (Spironolactone should be employed as the* ***first line drug)***
- ***Large volume paracentesis*** *should initially be carried out on patients with moderate or marked ascitis*
- ***Shunts (TIPS)*** *may be used in cases of Refractory Ascitis in whom recurrent paracentesis is too frequent or poorly tolerated, or in those with a hepatic hydrothorax*

## Cirrhosis and its Complications

### Cirrhosis: General

**110. Answer is A (chronic Hepatitis B):** *'Pathology: Basic and systemic' by Woolfe (1998)/587,597*

***Chronic viral hepatitis including Chronic Hepatitis B is associated with macronodular Cirrhosis and not micronodular cirrhosis.***
*Alcohol, hematochromatosis and large bile duct obstruction are all associated with micronodular cirrhosis.*

**Morphological Classification of Cirrhosis**

| Macronodular Cirrhosis (Parenchymal nodules > 3mm) | |
|---|---|
| **Aetiology** | **Frequency** |
| • *Chronic viral hepatitis* | *10-20%* |
| • *Wilson's disease* | *Rare* |
| • *α-Antitrypain deficiency* | *Rare* |
| • *Various drugs and toxins* | *Rare* |
| • *Hereditary haemorrhagic telangiectasis* | *Rare* |
| • *Cryptogenic cirrhosis* | *Common* |

| Micronodular Cirrhosis (Parenchymal nodules < 3mm) | |
|---|---|
| **Aetiology** | **Frequency** |
| • *Alcohol* | *60-70%* |
| • *'Primary' biliary cirrhosis* | *5%* |
| • *Large bile duct obstruction* | *<5%* |
| • *Haemochromatosis* | *5%* |
| • *Intestinal bypass* | *Rare* |
| • *Cystic fibrosis* | *Rare* |
| • *Indian childhood cirrhosis* | *Rare* |

**111. Answer is C (Gamma Globulins):** *Harrison 18th/p 2530 Harrisons 17th / 1925*

*Gamma Globulins are increased in chronic liver disease such as chronic Hepatitis and cirrhosis - Harrison*

**Gamma Globulins are produced by B Lymphocytes and not in hepatocytes**
*Gamma globulins are increased in chronic liver diseases such as chronic hepatitis and cirrhosis*
*In cirrhosis the increased serum gamma globulin concentration is due to the increased synthesis of antibodies, some of which are directed against intestinal bacteria, This occurs because the cirrhotic liver fails to clear bacterial antigens that normally reach the liver through the hepatic circulation*

**Alpha Globulins ($\alpha_1$ *and* $\alpha_2$) and Beta Globulins are produced primarily by hepatocytes**
*Their concentrations are thus likely to fall with impaired function of hepatocytes in chronic liver diseases like cirrhosis*

**112. Answer is D (Alpha-1 antitrypsin deficiency)**

***Alpha 1-antitrypsin deficiency is an inherited metabolic disorder that predisposes the affected individual to chronic pulmonary disease and chronic liver disease*** (cirrhosis, and hepatocellular carcinoma).

**Alpha-1 Antitrypsin Deficiency**

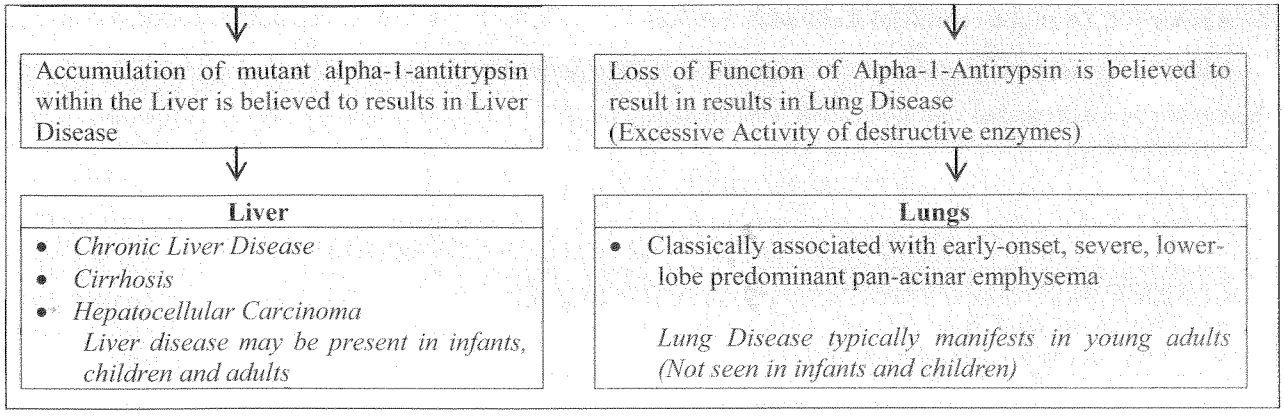
Alpha 1-antitrypsin deficiency is an inherited metabolic disorder
Alpha 1-antitrypsin deficiency is inherited as an autosomal recessive disorder with co-dominant expression
*The gene for alpha 1-antitrypsin is located on the long arm of chromosome 14, and has been mapped to 14q31–32.*

Alpha-1-Antitrypsin is a serine protease inhibitor ***secreted by the liver*** into the circulation where it is the main inhibitor of host tissue damage caused by Neutrophil Proteases released during acute inflammation

Alpha-1 antitrypsin deficiency is most commonly caused by Mutations in the SERPINA1 gene (Previously known as Pi gene for Protease inhibitor gene)

***Mutation in the gene encoding Alpha-1-Antitrypsin***
*(Polymers of Alpha-1-AT produced in the liver are unable to complete the secretory pathway for secretion into the cell)*

- Accumulation of Mutant Alpha-1-antitrypsin polymers in the endoplasmic reticulum of the liver
- Deficiency in the Concentration of Circulating Alpha 1-Antitrypsin




**113. Answer is D (Post necrotic cirrhosis):** *Harrisons 16th/ 858, 1859; Robbins 7th / 919*

***Post necrotic cirrhosis is charachterized by a shrunken liver with reduced liver span.***
*The normal liver span measures about 12- 15 cm and a lover span of 19cm suggests and chlorged liver. Presence of esophageal varices suggests portal hypertension due to advanced liver disease / cirrhosis or occlusion of portal vein.*

***Venoocclusive disease, Budd chiari syndrome, Hematochromatosis and Alcohol liver disease may all present with an enlarged liver and portal hypertension (esophageal varices).***

**114. Answer is E (Post necrotic cirrhosis):** *Robbins 7th/ 905, 967, 909, 911, 919, Harrisons 16th/ 858, 1859*

***Liver is typically shrunken in size and not enlarged in post necrotic cirrhosis.***
*Alcoholic hepatitis, NASH, Wilson's disease and Budd chiari syndrome may all present with enlarged liver and hepatocellular dysfunction.*

## Primary Biliary Cirrhosis & Sclerosing Cholangitis

**115. Answer is A (Pruritis):** *Harrison 15th/ 1757; Harrisons 16th/ 1860; Harrison 17th/ 1974 Harrison 18th/p 2595*

***'The earliest symptom is 'pruiritis' which may be either generalized or limited initially to the plams and soles.'***
*– Harrison*

**Primary Biliary Cirrhosis**

Primary biliary cirrhosis is a disease characterized by chronic inflammation and fibrous obliteration of intrahepatic bile ductules due to an unknown (primary) stimulus.

**Etiology / pathogenesis :**

PBC is believed to be due to an autoimmune [Q] etiology as it is often associated with other autoimmune disorders [Q] such as
1. CREST [Q] : **C**alcinosis, **R**aynaud's, **E**sophageal dysmotility, **S**clorodactyly Talenglectasia
2. SICCA SYNDROME [Q]
3. Autoimmune thyroiditis [Q]
4. Renal tubular acidosis

- Antimitochondrial Antibody (IgG) is positive

**Clinical feature :**

- Most patients are asymptomatic [Q]
- Pruritis is commonest / earliest symptom [Q]
- Jaundice [Q]
- Melanosis: gradual darkening of exposed areas of skin [Q]
- Deficiency of fat soluble vitamins due to malabsorption [Q]
  - Vit D deficiency : bone pain - osteomalacia [Q]
  - Vit K deficiency : bleeding – bruising [Q]
  - Vit A deficiency : Night blindness [Q]
- *Xanthelisman & xanthomas* [Q] due to protracted elevaliar of serum lipids.

**Lab Findings :**

- ↑↑ Serum alkaline phosphatase [Q] (2-5 fold)
- **Positive antimitochondrial antibody** :[Q] Sensitive and specific
- Hyperlipidemia [Q]

**116. Answer is C (Antimitochondrial Antibodies):** *Repeat*

***Antimitochondrial Antibodies are present in about 90 % of patients with Primary Biliary Cirrhosis.***

**117. Answer is A (Increased risk associated with smoking)** *CPDT 16th/ 675 CMDT 2008/707;09/622; Harrisons 17th/2001, 1975 Harrison 18th/p 2627, 2596*

***Smoking is associated with a decreased risk of developing primary sclerosing cholangitis (and not an increased risk)***
*'As in ulcerative colitis, smoking is associated with a decreased risk of primary sclerosing cholangitis' – CMDT*

Two important conditions with decreased risk from smoking

- *Ulcerative colitis (UC)*[Q]
- *Primary sclerosing cholangitis (PSC)* [Q]

**Primary Sclerosing Cholongitis**

Progressive Idiopathic obliteration of intrahepatic or extrahepatic bile ducts

**Note**
*Smoking is associated with a decreased risk of PSC (and UC)*[Q]

- *Most common in Men aged 20- 50 years (M > F)*
- *Characteristically associated with ulcerative colitis (IBD) (and less commonly with crohn's disease)*
- *Characteristic increased risk of cholangiocarcinoma (10%)*

| Presentation | Characteristic Laboratory Feature | Diagnostic study of choice |
|---|---|---|
| • **Progressive obstructive jaundice.** Patient presents with progressive jaundice, pruiritis and other features of cholestasis | • **GGT is typically elevated** ***Asymptomatic elevation of GGT is the earliest finding*** • **ALP & bile acids are ↑ed** | *ERCP or MRCP is the diagnostic study of choice demonstrating irregularities of the biliary tree* |

**118. Answer is A (Increased incidence in Females):** *CMDT 2008/603;09/622; CPDT 16th/675; Harrison 18th/p 2596 Harrisons 17th/2001, 1975 Refer previous question*

***Primary sclerosing cholangitis is characteristically more common in men than women***

*'PSC is most common in men aged 20 to 50 years' – CMDT*

**119. Answer is C (In advanced stages of cirrhosis major blood supply to liver comes from Hepatic vein)** *Harrison 18th/p 2595, 2596 Harrisons 17th/ 1974*

***In advanced stages of cirrhosis major blood supply to Liver comes from Hepatic artery and not from hepatic vein***

**Antimitochondrial Antibodies are positive in PBC** *(Harrisons 17th/ 1974)*
*'Antimitochondrial' Antibodies (AMA) are present in about 90% of patients with PBC' – Harrison*

**Elevated Lipoprotein Y is seen in PBC:** *Rubin's Pathology 5th/ 328*
*' The serum levels of cholesterol increase strikingly in PBC and an abnormal lipoprotein (Lipoprotein- x) appears which is found in many forms of chronic cholestasis' – Rubin's pathology*

**In Late stages of PSC treatment is Liver Transplantation** *(Harrisons 17th/1975)*
*'The ultimate treatment of PSC is Liver transplantation' – Harrison*

**In advanced stages of cirrhosis major blood supply to Liver is from hepatic artery**
Normally 80% of blood flow to liver comes from the portal vein and 20% of the blood supply is contributed by the hepatic artery

*In cirrhosis the blood flow to liver from the portal vein is reduced due to increased pressure and a compensatory increase in the blood to liver through the hepatic artery occurs*

***Hepatic veins drain blood away from the liver and do not contribute in the blood supply to the liver***

## Non Cirrhotic Portal Fibrosis

**120. Answer is D (Non cirrhotic portal fibrosis):** *API 6th 591; API 7th/ 621; Harrison 17th 621*

***Young patients presenting with features of portal hypertension along with a moderate/large splenomegaly with conspicuous absence of features of liver cell failure suggests a diagnosis of NCPF.***

| **NCPF is suspected in a patient presenting with symptoms of portal hypertension with:** |
|---|
| • YOUNG AGE<br>• Moderate/Large Splenomegaly<br>• ***NO*** FEATURES SUGGESTIVE OF LIVER CELL FAILURE<br>- No Jaundice (uncommon)<br>- No Ascitis (uncommon)<br>- No Hepatomegaly (uncommon)<br>- No Stigmata of liver cell failure (uncommon) |

**Non cirrhotic portal fibrosis** is a condition of liver characterized by widespread fibrosis of the liver (mainly portal, subcapsular and rarely perisinusuoidal) causing wide variation in the normal architecture but there is no true cirrhosis.

*NCPF is the most important causes of intrahepatic non cirrhotic portal hypertension in India.* Q

| INFECTION | Chemicals | Immune |
|---|---|---|
| – E. coli? | – Arsenic Q | mechanisms |
| – Malaria? | – Vinyl chloride Q | |

↓

Features of portal hypertension
- Gastrointestinal haemorrhage (most common symptom)
- Lump in abdomen (enlarged spleen)
- Splenomegaly is common (massive)

**121. Answer is A (EHPVO):** *'Tropical Hepato – Gastroenterology' by Tandon (Elsevier, India) 2007 /396, 397 'Non cirrhotic Portal Fibrosis: Current concepts and Management': Journal of Gastroenterology and Hepatology (2002) 17, 526- 534: 'Portal Hypertension : Pathogenesis & Management' by Helmy (2006) /354, 355; 'Comprehensive Clinical Hepatology' by Bacon, O,Gardy (2006) /553; 'Diseases of the Liver and Biliary System in Children' by Velly 3rd /559; 'Current Diagnosis & Treatment Surgery' by Doherty /537*

***Presence of hemetemesis, malena and splenomegaly suggests a diagnosis of portal hypertension. The most common cause of portal hypertension in a male child (12 year old boy) is Extra Hepatic Portal Vein Obstruction (EHPVO). EHPVO is therefore the single best answer by exclusion***

> ***Non Cirrhotic Portal Fibrosis*** *presents in a similar fashion clinically, however it is more common in females and in an adult population (third or fourth decade). NCPF is usually associated with a moderate/large (massive) splenomegaly*
> ***Cirrhosis*** *is an uncommon cause of portal hypertension in children and the absence of jaundice and ascitis makes this diagnosis more unlikely.*

*'An infant or child presenting with hemetemesis and mild/moderate splenomegaly in the absence of features of chronic liver disease is likely to be suffering from EHPVO. In adults, one needs to exclude diseases such as NCPF and compensated cirrhosis - 'Portal Hypertension': by Roberto De Franchis (Wiley - Blackwell) 2006 /314*

**Age of presentation favors a diagnosis of EHPVO over NCPF**

***Age at presentation is an important factor in distinguishing EHPVO from NCPF***

*- Indian Journal of Gastroenterology; 1984; Vol 3; No 4; 201-202*

| Features | EHPVO | NCPF |
|---|---|---|
| • Age | ***Children (1st & 2nd decade)*** | *Adults (3rd & 4th decade)* |
| • Gender | ***M > F*** | *F > M* |

| | | |
|---|---|---|
| • Variceal bleed (Hemetemesis / Malena) | + + | + + |
| • ***Splenomegaly*** | ***Mild /Moderate*** | ***Moderate / Large*** |
| • Jaundice / Ascitis Encephalopathy | *± (Absent / Transient)* | *± (Absent / Transient)* |
| • LFT | *Normal* | *Normal* |
| • Site of block along portal venous system | *Large branches are thrombosed (Main trunk; 1st order branches)* | *Small branches are involved (3rd order and 4th order branches)* |
| • USG | *Portal / Splenic vein block 'Portal covernoma'* | *Normal splenoportal axis* |

*'More than three quarters of Indian Children with portal hypertension were found to have extra hepatic portal vein obstruction (EHPVO) and Indian studies have shown extra hepatic portal vein obstruction (EHPVO) to be the commonest non cirrhotic cause for portal hypertension'*

*- 'Diseases of the Liver and Biliary System in Children' by Kelly 3rd /559*

*'In a prospective study 'Yaccha et.al' provided support for the hypothesis that the etiology of upper gastro intestinal bleeding in children may differ between developed and developing countries. They showed that 95% of children had upper gastrointestinal variceal bleeding, 92% of whom had bleeding due to EHPVO, a figure significantly higher than that seen in the west' - Disease of the Liver & Biliary system in Children by Kelly 3rd /560*

| Portal Hypertension in Indian Children | Portal Hypertension in Indian Young Adults |
|---|---|
| *The most common cause of Portal Hypertension in Indian Children is EHPVO* | *The most common cause of Portal Hypertension in Indian Adults is NCPF* |

**Absence of Jaundice and Ascitis makes a diagnosis of cirrhosis unlikely**

*Signs of Liver failure such as Jaundice and Ascitis are uncommon in EHPVO and NCPF. Their presence favors a diagnosis of cirrhosis and their absence makes cirrhosis unlikely*

Differentiating features between extrahepatic portal vein obstruction, non-cirrhotic portal fibrosis and cirrhosis of liver:

| Parameter | EHPVO | NCPF | Cirrhosis |
|---|---|---|---|
| Mean age (years) | 10 | 28 | 40 |
| Ascites | Absent/transient after bleed | Absent/transient after bleed | + to +++ |
| Encephalopathy | - | - | + |
| Jaundice signs of liver failure | - | - | + |
| Liver function tests | Normal* | Normal | Deranged |
| Liver<br>Gross<br>Microscopic | <br>Normal/small<br>Normal | <br>Normal, rarely irregular<br>Normal portal/fibrosis | <br>Shrunken, nodular<br>Necrosis, regeneration |
| Splenoportovenography/US | Portal/splenic vein blovk | Normal splenoportal axis, 'withered tree' appearance, periportal fibrosis | Dilated, patent portal and splenic vein |

*Occasional impairment may be observed
NCPF, non-cirrhotic portal fibrosis; EHPVO, extrahepatic portal vein obstruction; US, ultrasound

**122. Answer is B (Non cirrhotic portal fibrosis) :** *API 7th/621, 622; Various other texts;other texts*

***Features of portal hypertension in an adult with a large splenomegaly (8cm below coastal margin) with no history of jaundice or liver decompensation suggests a diagnosis of Non-cirrhotic portal hypertension.***

**Non cirrhotic portal hypertension** encompasses two distinct pathological condition that present with similar clinical features.

| |
|---|
| Non cirrhotic portal fibrosis |
| Extrahepatic portal obstruction |

*Distinction between the two conditions should ideally be made by further investigations as the similarly in presentation makes clinical criteria unreliable.*
*Neverthless if we do have to choose one single best option the following clues may be helpful.*

| NCPF | Extrahepatic portal hypertension |
|---|---|
| NCPF presents in young adults most commonly during the third and fourth decade | EHPH may present in two age groups<br>children (1st & 2nd decade) (congenital malformations)<br>Adults (4th & 5th decade) (thrombotic event) |
| **Mode of presentation** | |
| The onset of symptoms is gradual | The onset is gradual in children where the cause is congenital malformation<br>The onset is acute in adults where the cause is usually a thrombotic even |
| Mass in left upper quadrant (splenomegaly) is about 4 times more common in NCPF than EHPH | Mass in left upper quadrant (splenomegaly) is four times less common in patients with EHPH |

***Thus a young adult presenting with a gradually progressive cause and a moderate to massive splenomegaly suggests the diagnosis of Non cirrhotic portal fibrosis.***

**123. Answer is C (Non cirrhotic portal fibrosis):** *API 6th/ 591; API 7th/ 621*

*"Chronic ingestion of Arsenic has been incriminated in causation of NCPF. High Hepatic arsenic levels in patients with NCPF have been reported" – API 7th/ 621*

The precise etiology of NCPF remains an enigma.

**The implicated chemical agents include:**

1. Arsenic
2. Copper
3. Vinyl chloride

| Arsenic in also associated with the following cancers Q |
|---|
| 1. Skin cancer Q (Chandrasoma Taylor 3rd/ 285) |
| 2. Lung cancer Q (Chandrasoma Taylor 3rd/ 285) |
| 3. Hepatic angiosarcoma Q (Chandrasoma Taylor 3rd/ 185) |

**124. Answer is C (Upper gastrointestinal bleeding):** *Schwartz 7th/1420, 1421; www.emedicine.com/ RADIO/topic570.htm*

*Most common presenting symptom of extrahepatic portal hypertension is acute gastrointestinal bleeding.*

Acute gastrointestinal bleeding is the single best answer as explained below.

- ***'Hematemesis** resulting from bleeding esophageal varices is the most common presentation in patients with portal hypertension'- emedicine*
- ***Ascites** is not a usual accompaniment of extrahepatic portal venous obstruction, but has been noted occasionally.- Schwartz*
- ***Encephalopathy** rarely occurs in patients with obstruction of the extrahepatic portal venous system without hepatocellular dysfunction- Schwartz*
- ***Chronic liver failure** in the setting of portal hypertension suggests cirrhosis as the underlying cause. It is less likely with non-cirrhotic portal hypertension.*

**Note:**

***The most constant finding in patients with portal hypertension is splenomegaly (present in 80% of patients).***

*-CSDT 11th/580.*

*(Splenomegaly has not been provided amongst the options and hence upper gastrointestinal bleeding is the single best answer beyond any doubt.)*

## Portal Hypertension

**125. Answer is D (Sinusoids):** *Harrison 15th/e 1759; Harrison 16th/ 1863; Harrison 17th/ 1976 Harrison 18th/p 2597, 2598*

*'When cirrhosis is complicated by portal hypertension the increased resistance is usually sinusoidal'-Harrison's 15th/1759*

**Portal hypertension** (> 10 mm Hg: Normal portal pressure = 5 to 10 mmHg) most commonly results from increased resistance to portal blood flow.

**Increased resistance can occur at three levels:**

| Presinusoidal | Sinusoidal | Post sinusoidal |
|---|---|---|
| • Anatomically outside the liver eg. Portal vein thrombosis<br>• Within the liver but proximal to sinusoids eg. Schistosomiasis | ***Cirrhosis***<br>*When cirrhosis is complicated by portal hypertension, the increased resistance is usually sinusoidal* | • Outside liver, at level of hepatic veins<br>- ***Budd chiarri syndrome***<br>• In the inferior vena cava<br>- Thrombosis<br>• In the liver but distal to sinusoid<br>- Venoocclusive disease |

**Remember :**

1. Cirrhosis is the most common cause of portal hypertension in the United States.[Q]
2. Portal vein obstruction is the second most common cause. [Q]

**126. Answer is C (10-15 cm Saline):** *Harrison 14th/ 1710; Harrison 15th/ 1759; Harrison 16th/ 1863; Harrison 17th/ 1976 Harrison 18th/p 2597*

***Normal pressure in portal vein is low '10 – 15 cm saline'*** *– Harrison 14th/ 1710.*
***Normal pressure in portal vein is low '5 – 10 mm Hg'*** *– Harrison 16th/e 1863*

**Normal pressure in portal vein :**

| cm (Saline) | mm (Hg) |
|---|---|
| 10 – 15 cm saline | 5 – 10 mmHg |

**127. Answer is C (Esophageal varices) :** *Nelson 16th/e 1226*

***Presence of massive haematemesis in the background of moderate splenomegaly suggests a diagnosis of esophageal varices secondary to portal hypertension.***

**Esophageal varices :**

- *Most common presentation of esophageal varices is* ***Hematemesis.***
- ***'Splenomegaly****, sometimes with hypersplenism, is the next most common presenting feature in the portal vein obstruction.'*

**128. Answer is D (Oesophageal varices) :** *Read text below; Harrison 18th/p 2598 Harrison 17th 1976, Pretest Sugery 8th/ 8320*

***'Oesophageal variceal bleeding secondary to portal hypertension should always be the initial diagnosis in a young patient presenting with massive hematemesis and a moderate to large splenomegaly'***

**Features in favour of oesophageal varices:**

- Most common presentation of oesophageal varices is G.I. bleed, which may be 'massive'.
  - Massive hematemesis in children is almost always due to variceal bleed – Shwartz
  - Gastrointestinal bleed in peptic ulcer disease usually occurs in persons who are > 60 years old i.e. (it certainly is an uncommon presentation in a young boy) – Harrison
  - Erosive drug induced gastritis is usually superficial therefore hemodynamically significant 'massive' bleeding is rare
- Patients presents with moderate splenomegaly which is an important pointer towards presence of portal hypertension.
- Absence of any significant history of altered liver function in the presence of portal hypertension could well be attributed to an extrahepatic causes of portal hypertension.

**129. Answer is B (Esophagus varices)** *Harrison 16th /e p. 1863, 235, ; Harrison 18th/p 2598 Harrison 17th 1976-1977*

***'Massive haematemesis in the background of splenomegaly suggests variceal bleed due to portal hypertension.'***

**130. Answer is A (Portal Hypertension):** *Harrison 18th/320, 2598*

***Hemetemesis in a patient with palpable splenomegaly suggests a diagnosis of variceal blood secondary to portal hypertension.***
*Hemetemesis from Gastric ulcer, Mallory Weiss tear and/or drug induced gastritis is not associated with splenomegaly.*

**131. Answer is D (Acetic Acid):** *KDT 5th/ 560; API 7th/ 615; KDT 5th/560*

***Acetic acid has not been mentioned as a sclerosing agent.***

Sclerosing agents are irritants which cause inflammation, coagulation and ultimately fibrosis when injected into hemorrhoids or varicose vein mass. They are used only for local injection.
Endoscopic sclerotherapy involves local injection of sclerosants into variceal columns especially in lower 5 cm of oesophagus.

| These Sclerosing agents include: |
|---|
| 1. Polidocanal (Polydochyl) |
| 2. N butyl – cyanoacrylate (glue injection) |
| 3. Absolute alcohol & Phenol |
| 4. Ethalonalamine maleate / Oleate |
| 5. Sodium tetradecyl sulphate |

**132. Answer is B (Urgent endoscopy):** *Harrisons 16th/ 236; Harrisons 14th/ 248. ; Harrison 18th/p 2598, 2599, 320, 321 Harrison 17th 258, 1977*

*Acute episode of GI bleeding in a known patient of cirrhosis suggests a clear cut diagnosis of variceal bleed. **Urgent endoscopy is the modality of choice following haemodynamic stabilization as it is both a diagnostic and therapeutic modality.***

**Management protocol :**

| Cardinal principles of resuscitation<br>(**A**irway / **B**reathing / **C**irculation)<br>↓<br>**Urgent endoscopy**<br>(diagnostic + therapeutic modality)<br>Ligation is the endoscopic therapy of choice for variceal bleeding (Harrison 16th/236) |
|---|
| **Other options :** Endoscopic sclerotherapy Q /IV octreotide Q (Medical management) |

**Principles:**

- Once the patient is hemodynamically stable urgent endoscopy should be performed
- Ligation is the endoscopic therapy of choice for esophageal varices because it has requires fewer treatment sessions.
  - Less rebleeding
  - Fewer mortality rate
  - Fewer local complication
- Acute treatment with octreotide (preferred over vasopressin) is the medical management of choice
- In patients who have persistent or recurrent bleeding despite endoscopic and medical therapy, TIP is recommsended (TIPS is Transjugular intrahepatic portosystemic shunt)

**133. Answer is D (Bleeding from esophageal varices) :** *Multiple references*

***Sengstaken-Blakemore tube is a triple lumen tube used to tamponade (control) bleeding from esophageal varices.***

**134. Answer is B (Control around 90% of cases of variceal bleeding):** *Multiple references*

*Sengstaken-Blakemore tubes are used for the treatment of bleeding esophago-gastric varices. **Bleeding is controlled in up to 90% of cases** (at least for the duration of the insertion of the tube). Bleeding often recurs on deflation of the tube, hence definitive therapy is usually required*

**Sengstaken-Blakemore tubes do not have an Esophageal Aspiration Port (They have a Gastric Aspiration Port)**

*Sengstaken-Blakemore tubes have three lumens that include gastric balloon, oesophageal balloon and the gastric aspiration port.*

**The gastric balloon is inflated first (The esophageal balloon is rarely required)**

They are usually inserted via the nose in the same manner as a nasogastric tube. Once past the gastro-esophageal junction (> 55-60cm), ***the gastric balloon should be inflated first*** with air or water (after confirming the location)

The oesophageal balloon is rarely required but may be inflated in cases of intractable bleeding

*The gastric lumen should be regularly aspirated or placed on continuous low pressure suction. The balloon should be deflated every 12 hours but may be re-inflated it bleeding recurs. Sengstaken-Blakemore tubes should not stay in longer than 48 hours. The oesophageal balloon is rarely required. If used for cases of intractable bleeding, the balloon pressure should be kept below 40 mmHg and deflated every 1-4 hours to reduce the risk of oesophageal necrosis.*

**Weighted Traction should not be used**

Once the gastric balloon is inflated, gentle traction should be applied to bring the balloon to the gastro-esophageal junction. Taping the tube to the nose is generally sufficient traction. Weighted tubes increase the risk of necrosis of the gastric-oesophageal junction and nose.

**135. Answer is A (Upper GI bleeding)**

***Rockall risk scoring system attempts to identify patients at risk of adverse outcome following acute upper gastrointestinal bleeding***

| Common Risk Stratification Scores for Acute Upper GI Bleed |
|---|
| *Forrest Classification* |
| *Blatchford Risk score* |
| *Rockall Risk Score* |
| AIMS-65 Risk Score |

**136. Answer is A (Upper GI bleeding)**: *CMDT 2014/580*

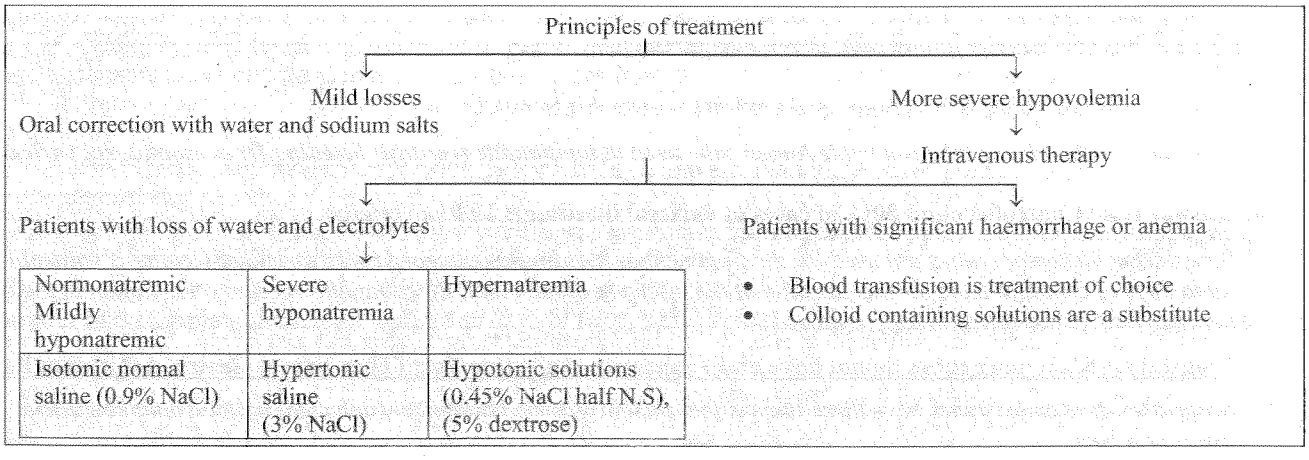
***Forrest classification is instrumental when stratifying patients with upper gastrointestinal hemorrhage into high and low risk categories for morality***. It is also a significant method of prediction of the risk of re-bleeding and very often is used for evaluation of the endoscopic intervention modalities

**137. Answer is A (Whole Blood transfusion is the best):** *Kumar & Clarke 5th/ 677; Harrison 16th/ 254; 15th/ 274; Harrison 17th/ 259 Harrison 18th/p 321, 322*

***'The overriding principle aim is to replace what is missing. Haemorrhage involves loss of whole blood, and the rationale treatment of acute haemorrhage therefore is the infusion of whole blood or a combination of red cells and a plasma substitute'*** *– Kumar Clarke 5th/ 677*

**Management of hypovolemia :** *Harrisons 16th/ 254; Kumar Clarke 5th/ 678.*

*The therapeutic goals are to restore normovolemia with fluid similar in composition to that lost and to replace ongoing losses.*




## Hepatic Encephalopathy / Hepatic failure

**138. Answer is D (Hepatitis E):** Sherlock's Diseases of the Liver and Biliary System (John Wiley & Sons), 2011/71

***Hepatitis E is the most common cause of Acute Liver Failure in India.***

*'In India, over 95% of acute liver failure is due to viruses, with 40% secondary to hepatitis E and 25–30% to hepatitis B' - Sherlock's Diseases of the Liver and Biliary System.*

- *Hepatitis E is the most common cause of Acute Liver Failure in India*
- *Hepatitis B remains the most common viral agent responsible for Acute Liver Failure Worldwide*
  - *Although Hepatitis E has a higher tendency to cause fulminant infection (1-2 %) in comparison to Hepatitis B infection (Up to 1%), Hepatitis B is the most common cause of fulminant infection overall since the overall incidence of Hepatitis B Hepatitis is higher than the incidence of Hepatitis E Hepatitis*
- *Tendency to cause acute liver failure (fulminant infection) is highest with HDV Superinfection on Chronic Hepatitis B and Hepatitis E infection in Pregnant women (up to 20 percent)*

**139. Answer is B (Hepatitis B):** *Sherlock's Diseases of the Liver and Biliary System (John Wiley & Sons), 2011/71*

***Hepatitis B remains the most common viral agent responsible for Acute Liver Failure Worldwide***

*Fulminant Viral Hepatitis leading to acute liver failure is typically seen with Hepatitis B infection (Increased by co-infection or super-infection with Hepatitis D) and Hepatitis E infection. The most common hepatitis virus responsible for fulminant disease and acute liver failure varies from one geographic region to the other. Hepatitis B is the most common cause of Acute Liver Failure in USA, Europe and Japan and accounts for a significant percentage of cases in the rest of the world thereby being the single most important virus implicated in Acute Liver Failure (Liver failure occurs in approximately 1 percent of patients with Acute Hepatitis B).*

*Note:*
*Hepatitis E is the most common cause of Acute Liver Failure in India*
*'In India, over 95% of acute liver failure is due to viruses, with 40% secondary to hepatitis E and 25–30% to hepatitis B. Hepatitis E is the most common cause of Acute Liver Failure in India*
*- Sherlock's Diseases of the Liver and Biliary System*

**140. Answer is C (Hyperkalemia):** *Harrison 14th/ 1715, 1716; 15th/ 1765 t; 16th/ 1868. ; Harrison 17th/1979 Harrison 18th/p 2601*

***It is Hypokalemia and not hyperkalemia that precipitates encephalopathy.***

***Hypokalemia*** *may contribute to systemic alkalosis and thereby cause an increase in the amount of non-ionic ammonia ($NH_3$), which readily crosses the BBB and accumulates in CNS worsening or precipitating encephalopathy.*

**Common precipitants of Hepatic Encephalopathy include :**

- Anaemia may lead to cellular hypoxia at the level of liver cells and thus ppt. encephalopathy Q
- Barbiturates are CNS depressant drugs and their injudicious use, therefore may precipitate hepatic Q encephalopathy.
- Hypothyroidism, though not mentioned as a direct precipitating. factor, may contribute towards precipitating encephalopathy by causing 'constipation' or slowing down the intellectual and motor activity.

| Increased nitrogen load as in | Electrolyte and Metabolic imbalance such as in |
|---|---|
| 1. *GI bleeding* Q | 1. *Hypokalemia* Q |
| 2. *Excessive dietary protein intake* Q | 2. *Alkalosis* Q |
| 3. *Azotemia* Q | 3. *Hypoxia* Q |
| 4. *Constipation* Q | 4. *Hyponatremia* Q |
| **Drugs** | **Miscellaneous conditions like** |
| CNS depressant agents like narcotics, tranquillizers, sedatives Q | Infection Q, surgery Q, superimposed acute liver disease. Q |

**141. Answer is D (Subcutaneous nodules):** *Chamberlain's Symptoms and Signs of Clinical Medicine 13th/382; Hepatology. Textbook & Atlas by Kuntz (Springer) 2008/84; Principles & Practice of Palliative Care & Supportive Oncology (Lippincott Williams) 2007/328*

***Subcutaneous nodules are generally not seen as a stigmata of chronic liver disease.***

*Chronic Liver Disease manifests with loss of subcutaneous fatty tissue resulting in paper thin skin with marked folds (paper-money skin).*

**Stigmata of Chronic liver Disease**

| Cutaneous | Nails and Hands | Male sex organ | Features of portal hypertension |
|---|---|---|---|
| • *Spider angiomata (telangiectasias)* | • *Muchrcke's nails* | • *Gynecomastia* | • *Splenomegaly* |
| • *Palmar erythema* | • *Terry's nails* | • *Testicular atrophy* | • *Ascites* |
| • *Jaundice (ictreus)* | • *Clubbing and hyperthrophic osteoarthroplathy* | | • *Caput medusa* |
| • *Paper money skin* | • *Dupuytren's contracture* | | • *Cruveilhier-Baumgarten murmur* |
| | • *Drumstick fingers* | | • *Fetor hepaticus* |
| | | | • *Asterixis* |

**142. Answer is D (Subcutaneous nodules):** *Chamberlain's Symptoms and Signs of Clinical Medicine 13th/382; Hepatology. Textbook & Atlas by Kuntz (Springer) 2008/84; Principles & Practice of Palliative Care & Supportive Oncology (Lippincott Williams) 2007/328*

***Subcutaneous nodules are generally not seen as stigmata of chronic liver disease.***

*Chronic Liver Disease manifests with loss of subcutaneous fatty tissue resulting in paper thin skin with marked folds (paper-money skin).*

**143. Answer is D (Subcutaneous nodules):** *Hepatology: Textbook & Atlas by Kunte (Springer) 2008/84*

***Subcutaneous nodules are not recognized as an established stigmata of Liver disease.***

*Parmar Erythema, Paper-money skin and Drum stick fingers are all established cutaneous stigma of chronic liver disease.*

Drum-Stick fingers can be observed in chronic liver patients with a hepatopulmonary syndromes. These changes are due to increased blood supply to the distal phalanges and the opening of av anastamoses with relative hypoxia to tissues as well as more extensive formation of connective tissue between nail and bone.

**144. Answer is D (Metabolic acidosis):** *Harrison 18th/p 2601; 17th/1979; 16th/1868, 1869; Refer previous question*

***Hepatic encephalopathy is precipitated by metabolic alkalosis and not by metabolic acidosis.***

**Electrolyte and Metabolic imbalances that precipitate Hepatic Encephalopathy**

*Hypokalemia*
*Alkaosis (Metabolic Alkalosis)*
*Hypoxia*
*Hyponatremia*

**145. Answer is A (Hyperkalemia):** *Harrison 18th/p 2601 Harrisons 17th /1979*

***Hepatic Encephalopathy is predisposed by Hypokalemia and not by Hyperkalemia***

**146. Answer is A (Hyperglycemia) :** *Refer text below; Current Gastroenterology Diagnosis & Treatment*

***Fulminant hepatic failure is associated with hypoglycemia and not with hyperglycemia***

*Hypoglycemia is a common complication of severe fulminant hepatic failure. The pathophysiology of hypoglycemia is multifactorial including impaired hepatic glucose release, impaired hepatic gluconeogenesis and elevated serum insulin levels. All patients with fulminant hepatic failure are recommended to recieve a continuous intravenous infusion of 10% dextrose to counteract hypoglycemia.*

| COMPLICATIONS IN ACUTE HEPATIC FAILURE | |
|---|---|
| **Metabolic** | **Neurologic** |
| *Hypoglycemia* | *Encephalopathy* |
| *Hypophosphatemia* | *Cerebral edema* |
| *Hypokalemia* | *Seizures* |
| *Hyponatremia* | *Intracranial hemorrhage* |
| *Hypomagnesemia* | **Multiorgan dysfunction** |
| **Acid-base disturbance** | *Pancreatitis* |
| *Respiratory alkalosis* | *Pulmonary edema / hemorrhage* |
| *Metabolic acidosis* | *Shock* |
| **Hematologic** | *Acute tubular necrosis* |
| *Aplastic anemia* | *Hepatorenal syndrome* |
| *Coagulopathy* | *Respiration failure* |
| *Disseminated intravascular coagulopathy* | *Sepsis* |
| **Ascitis** | |

**147. Answer is C (Increasing prothrombin time):** *Pediatric Hepatology (1990)/353; Harrison 18th/p 2530 Harrison's 17th/1926; Harrison's 16th /1816*

*It is difficult to choose one best prognostic factor as most criteria use a combination of various markers to assess the results.*
***Amongst the options provided the most important prognostic factors predicting survival is prothrombin time.***

*This is so because, coagulation factors have short serum half lives and their levels thus best determines the current status of liver function. The severity of hepatic lesion and mortality correlates best with the extent to which plasma levels of liver derived coagulation factors are depressed.* ***Prothrombin time*** *collectively measures factors II, VII, IX and X and gives a choice approximation of the extent to which these factor are depressed Marked prolongation of prothrombin time to > 5 seconds above control and not corrected by parentral vitamin K is a poor prognostic sign reflecting higher mortality and poor survival.*

Pediatric Hepatology (1990)/353
*'The standard liver blood tests (AST, ALT, ALP, Bilirubin, Ammonia) have no discriminatory value affecting survival The extent to which plasma levels of liver derived coagulation factors are depressed correlates with the severity of the hepatic lesion.'*

**148. Answer is D (Factor V estimation):** *API 7th/ 602; CMDT 2003/ 637; 09/592*

*It is difficult to choose one best prognostic factor as most criteria use a combination of various markers to assess the results.* ***However amongst the options provided 'factor V' estimation should be the choice to pick.***
*This is so because, coagulation factors have short serum half lives and their levels thus best determines the current status of liver function. The severity of hepatic lesion and mortality correlates best with the extent to which plasma levels of liver derived coagulation factors are depressed.*
*Prothrombin time which collectively measures factors II, VII, IX and X has not beenprovided amongst the options.*
*Levels of coagulation Factor V have also been shown to predict prognosis in patients with acute liver failure.*
*Accordingly perhaps 'Clinchy (France)' has use 'factor V levels' as an isolated prognostic marker in his criteria i.e. 'Clinchy criteria'*

**Clinchy Criteria (France)**

| |
|---|
| Factor V levels < 20% of normal in patients < 30 years of age |
| Factor V levels < 30% of normal in patients < 30 years of age |
| NB: The above factors indicate poor prognosis. |

| **Coagulation factors as Laboratory Prognostic markers in patients with acute liver failure include the following:** |
|---|
| 1. Prothrombin time (King's criteria) |
| 2. Factor V levels (Clinchy's criteria) |
| 3. INR (CMDT) |

**149. Answer is A (Prothrombin time (PT)):** *Schiff's diseases of the liver (Lippincott Williams, 2007)10th*

***An increased prothrombin time is the most frequently observed first laboratory test suggesting the possibility of hepatocellular failure. Early liver failure may be suspected based on isolated prolongation of the Prothrombin Time (PT).***

- **Prolonged PT** *is an early sensitive indicator of hepatic synthetic dysfunction due to the short half life of factor VII (2-6 hours) which the failing liver cannot maintain.*
- **APTT** *is prolonged after PT in Liver Disease.*
- **Albumin** has a long half life of about 20 days and hence reduced albumin will manifest only after 20 days of onset of Reduced synthetic function of Liver.
- **Increased arterial ammonia** is also a sign of acute liver failure, however increased arterial ammonia is primarily vieved as an important factor in the development of hepatic encephalopathy.

**Patients with early hepatocellular failure may present with isolated prolongation of PT**

*'Patient with liver disease may have only a prolonged PT (normal APTT and thrombin time) reflecting a decrease in factor VII which is the first to be reduced in liver disorders because of its short half life of 2-6 hours'*

*'Factor VIIa is an essential enzyme in the extrinsic pathway of coagulation. The pathway is evaluated by PT. Because factor VII has the shortest half life of the procoagulant proteins, patient with early liver disease may present with an isolated prolonged PT' - Hematology / Oncology Secrets / 82*

*'Increased Prothrombin Time has a high prognostic value, particularly for patients with acute hepatocellular failure. An abnormal prothrombin time with confirmed prolongation of more than 5-6 seconds above control is the single laboratory test that draws attention to the possibility of the development of flummant hepatic necrosis (acute hepato cellular failure) in the course of acute viral hepatitis. Such a prolonged prothrombin time often precedes by days the manifestations of liver failure' - Schiff's Disease of the Liver 10th/52*

*'Most coagulation factors are produced in the liver (except VWF) and development of liver disease may result in prolongation of both PT and APTT. However because factor VII (Extrinsic pathway; measured by PT) has the shortest half life amongst all vitamin K dependent factor, PT will be the first to be prolonged. Development of Liver disease will lead to deficiency of factor VII first and initial prolongation of only the Prothrombin Time. With further deterioration of liver function both the PT and APTT will be prolonged' - 'Clinical Anesthesia' by stoelting (Lippincott Williams) 2009/396*

**150. Answer is A (Hepatic encephalopathy):** *Harrison 16th/1868*

***Symmetric, high voltage, triphasic slow wave (2-5/second) pattern on Electroencephalogram (EEG) is characteristic (but non specific) of hepatic encephalopathy- Harrison 16th/1868***

| The diagnosis of hepatic encephalopathy should be considered when four major factors are present |
|---|
| 1. Acute or chronic hepatocellular disease and/or extensive portal systemic collateral shunts |
| 2. Disturbance of awareness and mentation which may progress from forgetfulness and confusion to stupor and finally coma. |
| 3. Shifting combinations of neurological signs including asterixis, rigidity, hyperreflexia, extensor plantar signs and rarely seizures. |
| 4. A characteristic but (nonspecific), symmetric, high voltage, triphasic slow wave (2 or 5/second) pattern on electroencephalogram. |

**151. Answer is D (Thyrotoxicosis):** *Marsden's Book of movement Disorders (Oxford Press) 2012/1008; Sapira's Art and Science of Bediside Diagnosis 4th/549*

***'Thyrotoxicosis (Hyperthyroidism) is associated with rapid fine tremors and not flapping tremors (irregular coarse tremor) also called Asterixis.***

*Asterexis (Flapping tremor) is most commonly seen in metabolic encephalopathies due to hepatic, renal (uremia) and respiratory failure ($CO_2$ Nercosis).*

**Causes of Asterixis /Flapping Tremor (Coarse irregular tremor)**

| **Typical Metabolic Encephalopathies** | |
|---|---|
| • ***Hepatic Encephalopathy*** | *Typically Metabolic Encephalopathies due to hepatic, renal and respiratory failure are the most common causes.* |
| • ***Uremic Encephalopathy*** | |
| • ***Respiratory failure with $CO_2$ Retention ($CO_2$ Narcosis)*** | |
| **Other Metabolic Encephalopathies** | |
| • *Hyperglycemia / Hypoglycemia* | |
| • *Electrolyte Disturbances (Hypokalemia, Hypomagnesemia etc)* | |
| **Medication side Effects / Intrications** | |
| • *Bromide intoxication* | • *Gabapentin / Pregabalin* |
| • *Phenytoin intoxication* | • *Valproate /Carbamazapine / Clozapine* |
| • *Chloral Hydrate intoxication* | • *Lithium / Levodopa* |
| • *Glutathemide intoxication* | • *Metrizamide / Ifosfamide* |
| • *Intravenous ammonium chloride* | |
| **Gastrointestinal Disease** | |
| • *Whipple's Disease* | |
| • *Malbsorption syndrome / Idiopathic Steatorrhea* | |
| • *Toxic Megacolon of Ulcerative Calitis* | |
| **Structural lesions** | |
| • *Vascular Infarction / Haemorrhage (brainstem / intraventruculer)* | |
| • *Subdural Empyema / hematoma* | |
| • *Encephalitis* | |
| • *Post-anoxic action myoclonus* | |
| • *Brain tumors* | |
| • *Post –surgical scars* | |
| **Miscellaneous** | |
| • *Congestive Cardiac Failure* | |
| • *Chronic Dialysis* | |
| • *Septisemia* | |

**152. Answer is B (Alzheimer's Disease):** *CMDT 2014/690; Multiple references*

***The Alzheimer type II astrocytes are not seen in Alzheimer's disease***

The Alzheimer type II astrocyte are greatly enlarged astrocytes with oval nuclei (vesicular and basophilic) that appear metabolically active. These Astrocytes are typically seen in Wilson's disease and hepatic encephalopathy. They may also be seen in urea cycle disorders and have been reported in canvan's disease (Canavan disease is also known as spongiform degeneration of white matter). ***The Alzheimer type II astrocytes are not seen in Alzheimer's disease***

**153. Answer is B (Autoimmune hepatitis):** *CMDT 2006/663,675; 09/597; Harrison 18th/p 2611, 2612 Harrison 17th/ 1987,1988; 16th/1877-1878*

***Amongst the options provided, recurrence of primary disease in the liver following liver transplantation is most common with auto immune hepatitis.***

*'Autoimmune hepatitis has been recognized to recur in upto 40% of transplanted livers as immuno supression is reduced.' - CMDT' 2006 / 663*

**Recurrance of primary disease following liver transplantation**

| **Auto immune Hepatitis** | **Primary billary Cirrhosis** | **Wilson's disease Alpha$_1$ –Antitrypsin deficiency** |
|---|---|---|
| Disease has been recognized to recur in upto 40% of transplanted livers as immunosupression is reduced *(CMDT)* | Disease recurs in the graft in 20% by 3 years' – *CMDT* | 'Hereditary disorders such as Wilson's disease and $\alpha_1$ antitrypsin deficiency have not recurred after liver transplantation' – *Harrisons 16/e, p 1878* |

## Hepatorenal Syndrome

**154. Answer is A & B (urine Na < 10 meq/l and Normal Renal Histology):** *Walker's Pediatric Gastrointestinal Disease 5th/1140; Washington Manual of Medical Therapeutics 32nd/506*

***Hepatorenal syndrome is associated with normal renal histology and supported by a urine sodium excretion < 10meq/L***

Hepatorenal syndrome

- Hepatorenal syndrome is defined as a state of functional renal failure (Reduced GFR) in patients with severe liver disease
- ***Structurally /Histologically the kidneys are normal and recover function after successful liver transplantation.***
- The pathogenetic hallmark of hepatorenal syndrome is intense renal vasoconstriction with coexistent systemic vasodilatation
- The diagnosis of hepatorenal syndrome is considered in accordance with the following diagnostic criteria.

| Diagnostic of Hepatorenal Syndrome |
|---|
| **Major criteria** |
| • *Low glomerular filtration rate, as indicated by serum creatinine > 1.5 mg/dL or 24-hr creatinine clearance < 40 mL/min* |
| • *Absence of shock, ongoing bacterial infection, fluid losses, and current treatment with nephrotoxic drugs* |
| • *No sustained improvement in renal function (decrease in serum creatinine to 1.5 mg/dL or increase in creatinine clearance to 40 mL/min) after diuretic withdrawal and expansion of plasma volume with 1.5L of a plasma expander* |
| • *Proteinuria <500 mg/dL and no ultrasonographic evidence of obstructive uropathy or parenchymal renal disease* |
| **Additional criteria** |
| • *Urine volume < 500 mL/d* |
| • *Urine sodium < 10 meq/L* |
| • *Urine osmolality greater than plasma osmolality* |
| • *Urine red blood cells <50/high- power field* |
| • *Serum sodium concentration < 130 mEqL* |
| Note: All major criteria must be present for the diagnosis of hepatorenal syndrome. Additional criteria are not necessary for the diagnosis but provide supportive evidence. |

**155. Answer is C (Urine osmolality is lower than plasma osmolality):** *Refer previous question*

***Hepatorenal syndrome is associated with urine osmolality greater than plasma osmolality (and not lower than plasma osmolality).***

*Creatinine clearance < 40 ml/minute and poor response to volume expansion are major diagnostic features of hepatorenal syndrome while urinary sodium of less than 10 mmol/L is an additional criteria that provides supportive evidence.*

**156. Answer is A > C (The creatinine clearance is > 40 ml/min) :** *Refer previous question.*

***Hepatorenal syndrome is associated with creatinine clearance < 40 ml/min which is a major criteria in the diagnsis of hepatorenal syndrome and the single best answer of choice***
*Hepatorenal syndrome is also associated with a urine osmolaity that is higher (and not lower) than plasma osmolality. However this is an additional or supportive criteria that is not necessary for diagnosis and hence this is not the answer of choice.*

## Hepatocellular Carcinoma

**157. Answer is D (Animal fat in diet):** *Harrison 16th/534, 527; Robbins 7th/924; Harrison 17th/ 580 Harrison 18th/p 777*

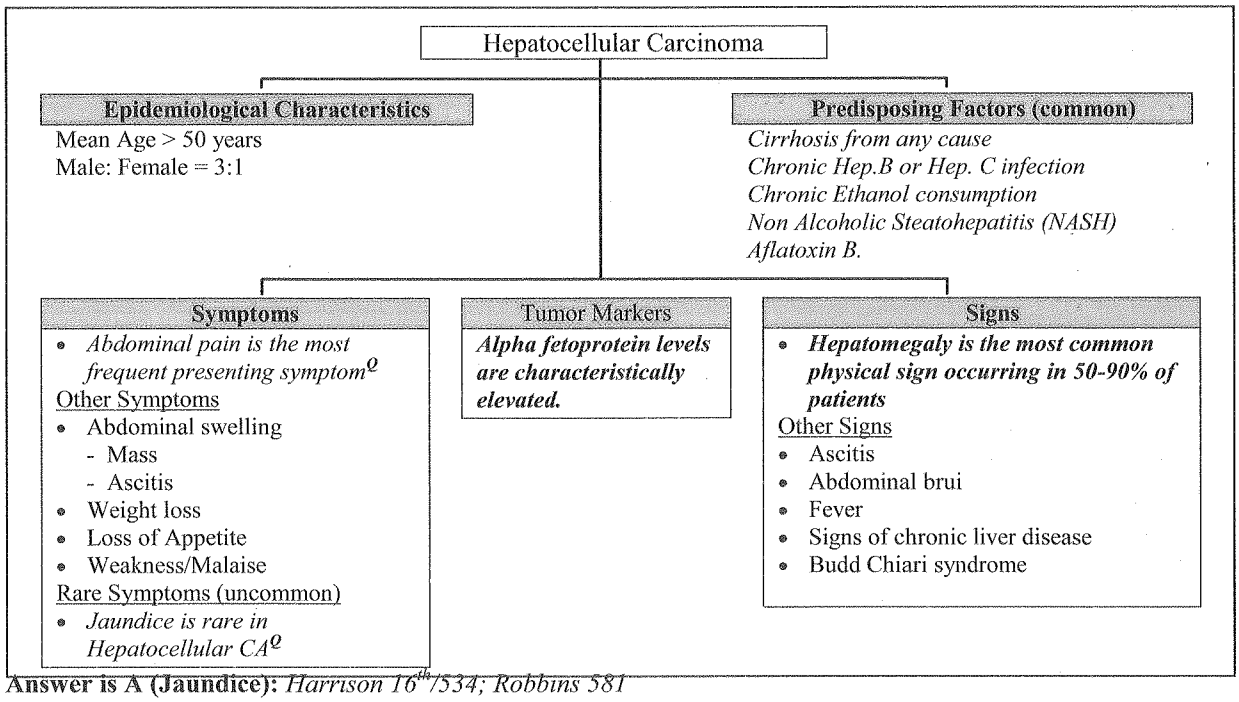
***Animal fat in diet is a known risk factor for development of colorectal cancer. It has not been mentioned as a risk for hepatocellular carcinoma.***

**Risk factors for hepatocellular carcinoma:**

| **Major etiological factors** - *Robbins* | **Other etiological factors** – *Harrison* |
|---|---|
| 1. Viral infection | Alphal antitrypsin deficiency |
| Hepatitis C infection | Hemochromatosis |
| Hepatitis B infection | Tyrosinemia |
| 2. Chronic alcoholism | Primary biliary cirrhosis |
| 3. Food contaminants: Alfatoxins | Exposure to thoriumdioxide or vinyl chloride |
| | Long term androgenic steroid administration |
| | Exposure to estrogen |

**158. Answer is B (Hepatocellular Carcinoma):** *Harrison 18th/p 777, 778, 779 Harrison's 17th/580,581,582*

***Presence of elevated Alphafetoprotein levels (tumor marker) and hepatomegaly (most common clinical sign) in a sixty year old patient with cirrhosis (predisposing factor) suggests the diagnosis of hepatocellular carcinoma.***




**159. Answer is A (Jaundice):** *Harrison 16th/534; Robbins 581*

***Jaundice is rare in hepatocellular carcinoma- Harrison***

| **Clinical manifestations of hepatocellular carcinoma:** |
|---|
| • Abdominal pain and Abdominal mass |
| - The most common presenting features are abdominal pain with detection of an abdominal mass I the right upper quadrant- *Harrison 16th/534* |
| • Ascites |
| - Blood tinged ascites occur in about 20% of cases – *Harrison 16th/534* |
| • Friction rub or brui: |
| - A friction rub or brui may be over the liver |
| • Malaise, fatigue, weight loss |
| **Uncommon / inconstant features** |
| • Jaundice |
| - Jaundice is ***rare***, unless significant deterioration of liver function or mechanical obstruction of bile duct occurs-*Harrison 16th/534* |
| • Esophageal variceal bleeding |
| - Gastrointestinal or esophageal variceal bleeding are ***inconstant*** findings – *Robbins* |

**160. Answer is A (Hepatocellular carcinoma) :** *Robbins 7th/926; Harrison 18th/p 779 Harrison 17th/ 582*

***Presence of elevated serum α fetopotein in the background of chronic history of alcohol consumption (risk factor for HCC) leads us to the diagnosis pf hepatocellular carcinoma.***
*AFP is the most specific and an ideal tumor marker for primary Ca of the liver i.e, Hepatocellular Carcinoma*
*The presence and persistence of high levels of serum AFP (Over 500 to 1000mg/L) in an adult with liver disease, and without an obvious gastrointestinal tumor strongly suggests Hepatocellular $C_A$.*

| **AFP levels as tumor marker** |
|---|
| 1. Liver cell carcinoma: Hepatocellular carcinoma |
| Hepatoblastoma |
| 2. Non seminomatous germ cell tumors of testes and ovary: |
| Choriocarcinoma |
| Embryonal carcinoma |
| Yolk sac tumors |
| Teratoma |
| Teratocarcinoma |
| 3. Gastrointestinal tumors |

***AFP levels may also be increased in non neoplastic conditions like cirrhosi & hepatitis.***

**161. Answer is A (Hepatoblastoma):** *Harrison 15th/590; 16th/535; Harrison 17th/ 582 Harrison 18th/p 779*

***Hepatoblastoma is a malignant liver tumor of infancy i.e. typically associated with very high serum AFP levels.*** *The lesions are usually solitary, may be resectable and have a better five year survival than that of HCC.*

**162. Answer is A (High levels are seen in fibrolamellar hepatic carcinoma):**
*- Harrison 16th/534; Chandrasoma Taylor 3rd/660; Harrison 17th 585 Harrison 18th/p 784*

***Fibrolamellar variant has no AFP elevation.***

- Fibrolamellar carcinoma is rare variant of hepatocellular carcinoma that occurs mainly in young adults and characteristically has no AFP elevation – *Chandrasoma Taylor 3rd/660*
- Alpha fetoprotein may be slightly elevated in some cases of hepatitis and cirrhosis – *Chandrasoma Taylor 3rd/660*
- Alpha feto protein may be found as a result of large metastasis from gastric (stomach) carcinoma or colonic carcinomas – *Harrisons*
- A rising level suggests progression of tumor or recurrence after hepatic resection or therapeutic approach such as ablation or chemoembolization.- *Harrison*

**163. Answer is A (Not common in Asians):** *Harrison, 15th/ 588; 16th/534; Harrison 17th/ 580 Harrison 18th/p 777*

***Primary hepatocellular carcinoma is specially prevalent in regions of Asia and Sub-Saharan Africa.***

- Primary hepatocellular carcinoma is specially prevalent in regions of Asia and Sub-Saharan Africa.
- The principal reason for high incidence of HCC in parts of Asia and Africa is the frequency of chronic infection with hepatitis B virus and hepatitis C virus. *Raised titres of HBV and HBC markers are thus important etiological predictors.*
- *Percutaneous liver biopsy is diagnostic* provided the sample is taken from an area localized by ultrasound or CT – *Harrison*
- *Fibromellar variant grows slowly and is associated with a longer survival if treated - Harrison*
  (It has thus a better prognosis)

**164. Answer is D (Has better prognosis):** *Harrison 15th 590; Chandrasoma Taylor 3rd/660, Robbins 7th/925; Harrison 17th/ 585 Harrison 18th/p 784*

***Fibrolamellar carcinoma grows slowly and is associated with a longer survival if treated. It has a distinctly better prognosis.***

| **Characteristic features of fibrolamellar carcinoma** |
|---|
| • Distinctive variant of Hepatocellular carcinoma |
| • Occurs in young adults (20 to 40 years of age) |
| • *Equal sex incidence (Robbins); More common in females -Chandrasoma Taylor* |
| • No association with HBV or cirrhosis |

- Well circumscribed mass (localized)
  *Non encapsulated but well circumscribed – Harrison*
  *Grossly encapsulated – Chandrasoma Taylor*
- No AFP elevation -*Chandrasoma Taylor*
- Better prognosis: Slow growth and longer survival.

**165. Answer is C (AFP levels always greater than 1000) :** *Harrison 14th/580, 15th//590, 16th / 535; Chandrasoma Taylor 3rd / 660; Harrison 17th/ 585 Harrison 18th/p 784*

***Fibrolamellar variant has no AFP elevation - Chandrasoma Taylor***
*Equal sex incidence - Robbins*
*More common in females -Chandrasoma Taylor*
***Although Robbins and Chandrasoma Taylor are contradicting each other as far as distribution of the tumor in the two sexes is concerned, elevation of AFP appears certainly not to be so significant as to rise to levels greater than 1000. The single best answer is undoubtedly option 'C'.***

## Budd Chiari Syndrome

**166. Answer is A (Hepatic vein obstruction):** *Harrison 14th/ 1709; 15th/ 1759; 16th/ 1862; Robbins 7th/ 919; 6th/ 883; Harrison 17th/ 733*

***Budd chiari syndrome by definition is 'occlusion of hepatic vein'.***

*Obstruction of two or more major hepatic veins produces Budd chiari syndrome*
*Obstruction of a single main hepatic vein by thrombosis is clinically silent*

**Budd Chiari Syndrome:**

- It is a clinical complex characterized by -
  - Liver enlargement (hepatomegaly)
  - Ascitis
  - Abdominal pain
- It is produced as a result of obstruction of two or more major hepatic veins and results from increased intrahepatic blood pressure and an inability of the massive hepatic blood from to shunt around the blocked outflow tract
- The most common cause of hepatic vein obstruction producing Budd chiari syndrome is hepatic vein thrombosis.

*It may also result from occlusion of IVC such as invasion by a tumour but this is certainly less common.*
*Idiopathic membranous obstruction of IVC is the most common cause of this syndrome in Japan.*

**167. Answer is D (Polycythemia vera):** *Robbins 6th/ 883; 7th/919; (Not elaborated in sequential order in Robbins 7th)*

***Amongst the options provided Polycythemia vera is the commonest cause of Budd chiary syndrome.***
*Budd chiari syndrome includes acute, subacute or chronic occlusion of hepatic vein most commonly caused by hepatic vein thrombosis.*

**Hepatic vein thrombosis is associated with in decreasing order of frequency:** *Robbins 6th/ 883*

- Polycythemia vera Q
- Pregnancy
- Postpartum state
- Use of oral contraceptives
- Paroxysmal nocturnal hemoglobinuria (PNH) Q
- Intraabdominal cancers, particularly hepatocellular carcinoma.

**168. Answer is C (Paroxysmal nocturnal hemoglobinuria):** *Robbins 6th/ 1883: Previous question.*

***The most common cause of hepatic vein thrombosis from the list mentioned in the previous question amongs the above is Paroxysmal nocturnal hemoglobinuria, and hence is the answer of choice here.***

**169. Answer is D (Thrombosis of hepatic veins):** *Refer previous question.*

***Most common cause of Budd Chiari Syndrome is hepatic vein obstruction***
***Most common cause of hepatic vein obstruction causing Budd Chiari Syndrome is 'thrombosis of hepatic veins'.***

**170. Answer is C (Hepatic vein):** *Refer previous question*

***Budd chiari syndrome is characterized by post sinusoidal obstruction outside the liver at the level of hepatic veins*** *– Harrison*

**171. Answer is D (Venous collaterals):** *CMDT 2014/ 697*

***Venous Collateral are not seen in Acute form of Budd Chiari Syndrome as they have not yet developed. Venous collaterals are typical findings in subacute and chronic forms of Budd Chiari Syndrome***
*Acute form of **Budd-Chiari** Syndrome follows sudden venous occlusion aresents with **acute** abdominal pain (Upper quadrant pain), vomiting, **tender hepatomegaly**, and **ascites.** Mild jaundice with elevated liver enzymes may be present. In acute **Budd-Chiari** syndrome, **collateral venous** channels have **not** yet developed*

## Disorders of Biliary Tract

**172. Answer is D (Cholestatic diseases) :** *Harrison 16th/1815; Harrison 17th/ 1925 Harrison 18th/p 2529*

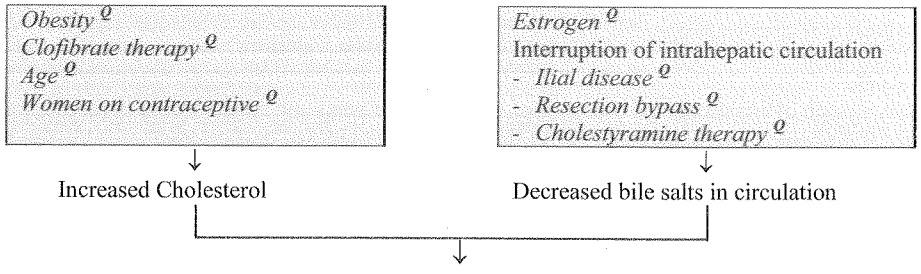
***5' Nucleotidase reflects cholestasis and is rarely elevated in conditions other than liver disease.***

| Most important enzymes reflecting cholestasis |
|---|
| • Alkaline phophatase |
| • 5' Nucleotidase |
| • Gamma Glutanym transpeptidase |

*5' Nucleotidase and GGT are the most specific marker for cholestasis and are rarely elevated in conditions other than liver disease - Harrison*

**173. Answer is A (Decreased Bile and Increased cholesterol ratio):** *Harrison 16th/1881, 1882; Harrison 17th/ 1991, 1992*

Bile salts and phospholipids in bile keep cholesterol in solution by the formation of micelles.
An ***excess of cholesterol relative to bite salts and phospholipids*** allows cholesterol to form crystals and such bile is called ***Lithogenic or Super-saturated bile.***




**174. Answer is D (Hypercholesterolemia):** *Harrison 14th/1728; 15th/1781; 16th/1881, 1882; 17th/ 1992, 1993 Harrison 18th/p 2617, 2618*

*It is increased concentration of cholesterol relative to bile salts in bile that promotes gall stone formation. Serum cholesterol may well be normal.*

***All other options are known local factors that promote gall stone formation and hence Hypercholesterolemia is the single best answer of exclusion.***

Formation of Gall stones is promoted by following factors :

1. ***Increased concentration of cholesterol*** relative to bile salts **in bile.** (***With or without hypercholesterolemia***)
2. Stasis
3. Infection

**Clofibrate therapy** :
This drug is used to excrete cholesterol in hyperlipoprotenemia
It therefore increases the concentration of cholesterol in bile.

**Hyperalimentation** :
Parental supplementation leads to hypofunction of Gall bladder, thus contibuting to gall stone formation by 'Stasis'.

**Primary biliary cirrhosis** :
Leads to a decrease in bile acid secretions. Decreased salts are unable to keep cholesterol in solution and therefore lead to precipitation of cholesterol stones

**175. Answer is D (Vagal stimulation):** *Bailey 23rd/975; Repeat*

*Stone formation is enhanced by Truncal vagotomy (not by vagal stimulation).*
*Vagotomy promotes stasis of bile by inhibiting gall bladder contractility and promotes stone formation.*
*All other options have been explained in the previous questions.*

**176. Answer is B (Ileal resection):** *Refer previous question*

*Ileal resection is an established factor for gall stone formation.*

*Ileal resection is associated with interruption of enterohepatic circulation of bile salts thereby decreasing the ratio of bile salts to cholesterol within the bile (Lithogenic bile)*

**177. Answer is D (More common in males between 30-40 years of age):** *Bailey and Love 24th/1103; 23rd/974*

*Cholelithiasis is more common in women than men*

**Lithogenic bile is required for gall stone formation and gall stones.**
May be associated with increased risk of carcinoma gall bladder.

***Diabetes mellitus** is associated with Gall bladder hypomotility which may contribute to increased incidence of gall stone in diabetics.*

**178. Answer is C (Terminal ileum):** *Love &Bailey 23rd/1066; Harrison 14th/1732,15th/1783, 16th/1886; Sabiston 16th/1095;*

*'Classically there is obstruction / impaction about 60 cm proximal to ileocaecal valve'* - Bailey
***'The site of obstruction by the impacted gall stone is usually at the ileocaecal valve" provided that the more proximal S.I. is of normal calibre.*** *- Harrisons*
*If both choices come simultaneously in a question go for 60 cm proximal to ileacoecal valve, as, it has been defined as the narrowest part of small intestine.*

**179. Answer is C (Ileum):** *Refer previous question*

*Thye most common site of obstruction due to gall stone is the terminal ileum.*

**180. Answer is B (Duodenum 1st part):** *Hamilton Bailey 10th/432; Diseases of Gall bladder and Bile duct 1st/188*

*The most common site of Biliary – enteric fistulas is the duodenum (Cholecystoduodenal fistula)*

| Type of fistula | Percent | Comment |
|---|---|---|
| Cholecystoduodenal | ≈ 75% | Most common type (duodenum) |
| Cholecysto colic | ≈ 16% | Second most common (colon) |

**181. Answer is A (Observation) :** *Bailey 23rd/974; Harrison 14th/1729, 15th/1780; 16th / 1884*

*Prophylactic cholecystectomy is not warranted in an asymptomatic patient. As the question does not provide us with any details to decide upon the possibility of medical therapy observation remains the management of choice.*
Gallstone disease in an asymptomatic patient or in a patient whose symptoms are not referable to cholelithiasis is called ***'Silent' or Asymptomtic Gallstones***, & is a common clinical problem.
*Prophylactic cholecystectomy is not warranted.*
*This also applies to Diabetes with silent Gallstones.*

**182. Answer is D (55 year old with an asymptomatic gallstone):** *Refer previous question*

*Prophylactic cholecystectomy is not warranted in an asymptomatic patient.*

**183. Answer is C (No surgery for gallbladder stones):** *Refer previous question*

*Prophylactic cholecystectomy is not warranted in an asymptomatic patient.*

**184. Answer is A (Size of stone less than 15mm) :** *Harrison 14th/1730; Harrison 15th/1781; 16th / 1884; Harrison 17th/ 1995*

*Harrison 18th/p 2621*

***Medical therapy for gall bladder stone is amenable for stones < 15 mm (preferably <10 mm)***

| Prerequisites for medical therapy : |
|---|
| *1. Gall bladder should be functioning* Q |
| *2. Stones should be radioluscent* Q |
| *3. Size should be small preferably < 15 mm* Q *- Harrison 14th (<10mm-Harrison 16th)* |
| *4. Stones should be 'cholesterol stones' only (obvious by thier mechanism of action)* Q |

(*Newer edition of Harrison has mentioned the size of stone to be preferably < 10 mm rather than < 15 mm but we will go with same answer because the question was framed in older times*).

| Medical therapy for Gall stone dissolution consists of administration of : |
|---|
| *UDCA (Ursodeoxycholic acid)* Q |
| *CDCA (Choledeoxycholic acid)* Q |

**Mechanism of action:**
*Inhibit HmG CoA reductase activity* Q, which in turn results in decreased hepatic cholesterol synthesis.
Allows dispersion of 'cholesterol' from stones by physicochemical means.

**185. Answer is A (Motor mechanisms of Gall bladder):** *Bailey 23rd / 967*

***Functioning motor mechanism of the gall bladder is not a prerequisite*** Q***, & even in its absence, the contrast can be concentrated in the Gall bladder & be visible radiographically.***
**Oral Cholecystogram** (also called *Graham Cole test*) Q

- *Ipanoid Acid tablets* Q (contrast) is taken the right before the test.
- The contrast is absorbed, secreted into the bile by the liver (i.e. *functioning hepatocytes required*) Q passes through the cystic duct into the gal bladder (i.e. *patent cystic duct is required*). But is then concentrated in the Gall Bladder (ability to absorb water is required)
- *Functioning motor mechanism of the gall bladder is not a prerequisite* Q, & even in its absence, the contrast can be concentrated in the Gall bladder & be visible radiographically.
- Since *a negative test can result from so many causes, it is NOT diagnostic of Gall stone Disease.* Q

**186. Answer is A (Renal stones):** *Bailey 23rd/975*

***Renal stones are not a feature of Saint's triad***

| Saint's triad (Association of) |
|---|
| Diverticular disease |
| Gall stone/Cholelithiasis |
| Hiatus Hernia |

**187. Answer is D (Vomiting):** *Clinical Surgery by Thompson/289*

Charcot's triad constitute the classical presentation of acute cholangitis and includes:

| Charcot's triad |
|---|
| Abdominal pain |
| High fever with rigors |
| Jaundice |

**188. Answer is D (Hemobilia) :** Diseases of the Gallbladder and Bile Ducts: Diagnosis and Treatment (John Wiley & Sons, 2008)/ 247; *Harrison's 18th/ Chapter 311*

***Hemobilia is not a feature of Mirrizi Syndrome.***

**Mirizzi syndrome** is a manifestation of the impaction of a gallstone in the cystic duct at the gallbladder neck that results in extrinsic compression/ obstruction of the common hepatic duct/bile duct, causing jaundice and/or causing erosion of the wall of the common hepatic duct/bile duct resulting in cholecystocholedochal fistula. Obstructive jaundice is the key feature of Mirizzi's syndrome and is frequently accompanied by right upper quadrant abdominal pain and fever often suggesting a diagnosis of acute cholangitis. Ultrasound shows gallstone lying outside the hepatic duct. Endoscopic retrograde cholangiopancreatography(ERCP) or magnetic resonance cholangiopancreatography (MRCP) will usually demonstrate the characteristic extrinsic compression of the CBD. Surgery remains the treatment of choice for Mirrizi syndrome

| | |
|---|---|
| **Type 1** | External compression of the common hepatic duct (CHD) or common bile duct (CBD) by a calculus impacted in the cystic duct (Hartmann's pouch or at the neck of the gallbladder) causing jaundice |
| **Type 2** | Erosion of the wall of the common hepatic duct causing a cholecystocholedochal fistula |

**189. Answer is B (Acute Cholecystitis):** *The Trauma Manual: Trauma and Acute Care Surgery*

***The Tokyo guidelines provide guidance regarding diagnosis, severity assessment and management of acute cholecystitis and acute cholangitis (biliary diseases)***

**190. Answer is A (CBD stone) :** *Harrisons 14th/580, 15th/590; 16th/536; Harrison 17th/ 585 Harrison 18th/p 784*

*Cholelithiasis is not clearly a predisposing factor for Cholangiocarcinoma - Harrison*

| ***The predisposing factors of cholangiocarcinoma include :*** |
|---|
| 1. Chronic hepato-biliary parasite infection $^{Q}$ |
| (Clonorchiasis or Asiatic cholangio-hepatitis) $^{Q}$ |
| 2. Congenital Anomaly with ectatic ducts (Choledochal cyst). $^{Q}$ |
| 3. Sclerosing cholangitis $^{Q}$ |
| 4. Ulcerative colitis $^{Q}$ |
| 5. Occupational exposure to carcinogens $^{Q}$ (Rubber + Automotive plants) |

**Note:** *Nodular lesions that arise at the bifurcation of hepatic ducts are called* ***Klastskin tumors***$^{Q}$.

**191. Answer is D (Chronic pancreatitis) :** *Refer previous question; Harrison 17th/ 585 Harrison 18th/p 784*

***Chronic pancreatitis does not predispose to cholangiocarcinoma.***

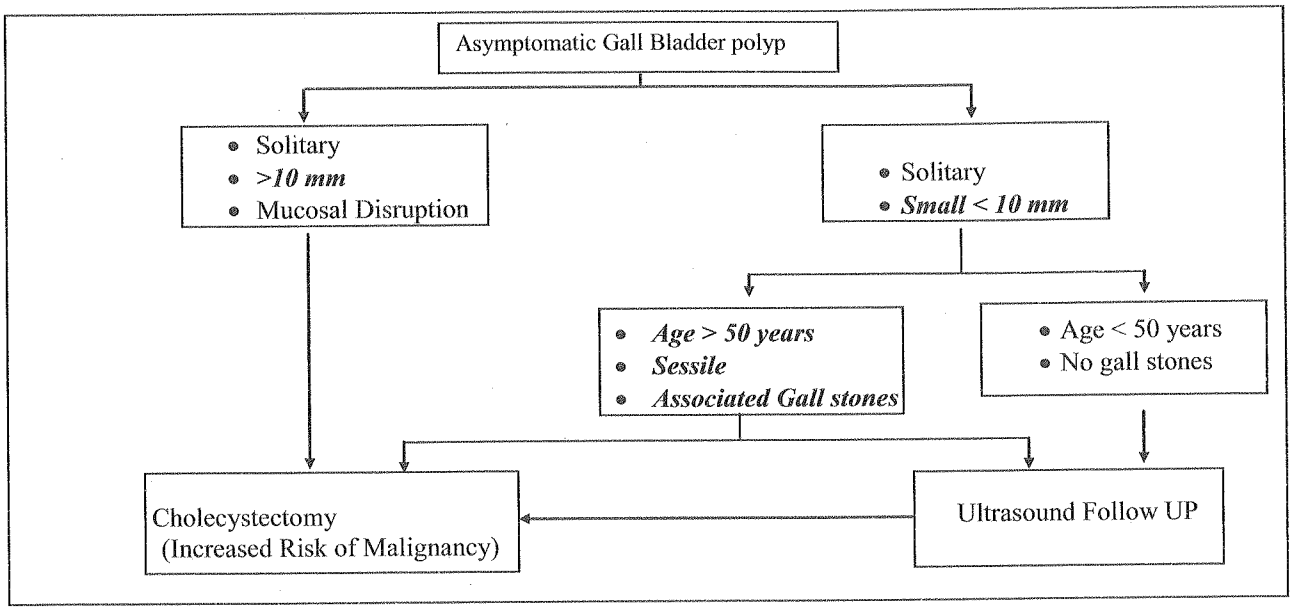
**192. Answer is C (Size of polyp > 5mm)** *Schwartz 8th / 1214, Manual of Gastroenterology 4th/ 457; 'Mastery of surgery' by Fischer 5th/ 1025, Basis and New Aspects of Gastrointestinal Ultrasonography' (2005)/117*

***Risk factor for malignant change in an Adenomatous Gall bladder polyp is a size greater than 1.0 cm (10mm). Polyps smaller than 1.0 cm seldom undergo malignant transformation.***

*'Malignancy should be considered when polyp exceeds 1 cm in diameter or when rapid growth of polyp is seen on sonographic follow-up' - 'Diagnostic Ultrasound' by Goldberg – 2nd/ 454*

| **Factors which indicate possibility of malignancy in Gall bladder polyps** |
|---|
| • *Age > 50 years*$^{Q}$ |
| • *Presence of a single polyp*$^{Q}$ |
| • *Sessile Polyps*$^{Q}$ |
| • *Polyp > 1.0 cm in size*$^{Q}$ |
| • *Rapid change in size of polyp*$^{Q}$ |
| • *Associated Gall stones*$^{Q}$ |

(*Taken from 'Basic and New Aspects of Gastrointestinal Ultrasonography* (2005 / 117) )




## Wilson's Disease and Hemochromatosis

**193. Answer is B (Increased Ceruloplasmin) :** *Harrison 15th / 2274; 16th/2314; 17th/ 1981, 1982 Harrison 18th/p 2604*

***In Wilson's disease, Ceruloplasmin levels are decreased (not increased).***

*In Wilson's disease excess Cu saturates liver and spills in the plasma thereby decreasing ceruloplasmin levels. (Serum Ceruloplasmin is ↓↓ Q)*

| Serum Ceruloplasmin levels | |
|---|---|
| Normal | 180-350mg/L (18-35 mg/dl) |
| Wilson's Disease | Low in 90% |

Basic defect in Wilson's disease - Reduced biliary excretion of Cu
(mutation of gene on chromosome 13 which promotes Cu excretion)
↓ (*Autosomal recessive*) (ATP 7B gene)

***Accumulation of Cu in Hepatocytes***

*Coombs negative hemolytic anemia* Q is seen
*Renal tubular acidosis* Q, though rare, may be seen

*All form of hepatitis* (including fulminant type)
- Acute hepatitis
- Fulminant hepatitis
- ***Chronic active hepatitis***
- Cirrhosis

Cu saturates liver, spills in plasma and is spread to other systems
(***Serum Ceruloplasmin is ↓↓*** Q)

| CNS | Eyes | Genital | Kidney | Psychiatric changes |
|---|---|---|---|---|
| ***Deposits in Basal Ganglia*** Q<br>Neurological manifestations<br>- *Tremors: resting / intention* Q<br>- Spasticity / Rigidity<br>- *Chorea* Q<br>- Drooling/Dysphagia/Dysarthria<br>**Sensory Changes Never Occur** | ***Copper gets deposited inDescemet's*** Q ***membrane of cornea*** Q<br>*'Kayser* Q *Fleischner' ring* (KF rings do not interfere with vision) Q<br>*Sunflower cataract* Q | - Free copper in intrauterine secretions<br>- Primary or Secondary Amenorrhea Q<br>- Recurrent abortions Q | - Microscopic Hematuria,<br>- Nephrocalcinosis<br>- Renal calculi | - Loss of emotional control,<br>- Depression,<br>- Hyperactivity,<br>- loss of sexual activity. |

**194. Answer is C (Pronounced Sensory Changes):** Harrison 18th/ 3188; Refer Wilson's Disease Review

***Sensory changes are not seen in Wilson's disease.***

*Sensory abnormalities and muscular weakness are not features of Wilson's Disease' – Harrison 18th/3188*

**Neurological manifestations of Wilson's disease include Tremors**

*Neurological manifestations of Wilson's disease result from deposition of Copper in the basal ganglia and occasionally in the pons, medulla, thalamus cerebellum and subcortical areas.*

| *Movement Disorders* | *Autonomic Disturbances* | *Others* |
|---|---|---|
| *Three types of movement disorders may be seen:*<br>• *Dystonia*<br>• *Incoordination*<br>• *Tremor* | • *Orthostatic Hypotension*<br>• *Sweating abnormalities*<br>• *Bowel dysfunction*<br>• *Bladder dysfunction*<br>• *Sexual dysfunction* | • *Migraine Type Headaches*<br>• *Memory loss*<br>• *Difficulty focusing on tasks (but cognition is usually not grossly impaired)* |

*Dysarthria and dysphagia are common.*

**Renal calculi and Sunflower cataracts may be seen in Wilson's disease**

*'Sunflower cataracts and Kayser-Fleischer (KF) Rings may be seen' – Harrison*
*'Cholelithiasis and Nephrolithiasis (Renal Stones) occur with increased frequency'- Harrison*

**195. Answer is A (Autosomal Dominant Inheritance):** *Harrison 18th/3188; Refer Wilson's Disease Review*

*Wilson's disease is inherited as an autosomal recessive disorder.*

*Basic defect Wilson's disease is reduced biliary excretion of copper from a mutation of gene on chromosome 13 which promotes copper excretion. Serum ceruloplasmin levels are decreased. Coombs negative haemolytic anemia may be seen.*

*The association of hemolysis and liver disease makes Wilson's Disease a likely diagnosis - Harrison*

**196. Answer is B (Low serum ceruloplasmin and high urinary copper)** : *Harrison 18th/p 3189 Harrison's 17th/2450*

***Wilson's disease is associated with low levels of serum ceruloplasmin and high urinary copper excretion***
*The basic defect in Wilson's disease is reduced biliary excretion of copper* due to a mutation of gene on chromosome 13 which promotes copper excretion. This leads to accumulation of copper initially in the liver and subsequently in plasma and other systems once liver is saturated. *Serum ceruloplasmin is the main copper binding protein in the blood and once excess copper spills into the blood,* ***levels of free ceruloplasmin are decreased.*** *Also excess copper is eventually excreted in urine and hence* ***urinary copper levels are increased or high.***

**Useful Tests for Wilson Disease:**

| Test | Wilson's Disease | Normal Value | Comment (Wilson's Disease) | Usefulness |
|---|---|---|---|---|
| *Serum ceruloplasmin* | ***Decreased*** | 180-350mg/L (18-35 mg/dL) | Low in 90% | + |
| *KF rings* | *Present* | Absent | Present in 99% if neurologic or psychiatric symptoms present<br>Present in 30-50% in hepatic presentation/presymptomatic state | ++ |
| *24-h urine Cu* | ***Increased*** | 0.3-0.8 μmol (20-50 μg) | >1.6 μmol (>100 μg) in symptomatic patients<br>0.9 to >1.6 μmol (60 to > 100 μg) in presymptomatic patients | +++ |
| *Liver Cu* | *Increased* | 0.3–0.8 μmol/g (20-50 μg) | >3.1 μmol (>200 μg)<br>(obstructive liver disease can cause false-positive results) | ++++ |
| *Haplotype analysis* | *2 Matches* | 0 Matches | 2 Matches | ++++ (Siblings only) |

**197. Answer is B (Wilson's Disease):** *Harrison 18th/p 3188 Harrisons 17th/2449, 2450; Harrisons 16th/2313,2314; Refer previous question*

***Psychiatric manifestations in the form of emotional lability along with neurological manifestations in the form of tremors and the characteristic 'Kayser Fleisher Rings' (golden brown discolouration of descemet's membrane) are diagnostic of Wilsons disease.***

**198. Answer is B (Testicular Atrophy):** *Harrison 18th/p 3187, 3188 Harrisons 17th/2449, 2450, 2451; Harrisons 16th/2313,2314*

***Testicular Atrophy is not documented as a feature of Wilson's disease.***
***Hemolytic Anemia, Chorea and Chronic active hepatitis are documented manifestations of Wilson's disease.***

**Hemolytic Anemia is a feature of Wilson disease**
*Hemolytic Anemia may occur in severe hepatic failure because large amounts of copper derived from Hepatocellular damage are released into the blood stream.*
*'The association of hemolysis and liver disease makes Wilson's a likely diagnosis'- Harrison*

**Chorea is a feature of Wilson's disease**
*Chorea is an established Neurological manifestation of wilson's disease*

**Chronic Active hepatitis is a feature of Wilson's disease**
*Wilson's disease may present as fatty change, acute hepatitis, chronic active hepatitis, cirrhosis or massive hepatic necrosis.*

**199. Answer is C (Wilson's disease):** *Harrison 18th/p 3188 Harrisons 17th/ 2450; Greenberg's Text Atlas of Emergency Medicine (2005)/114*

***KF rings are a charachteristic feature of Wilson's disease.***

**Kayser – Fleischer Rings (KF Rings)**

- *Brownish yellow discolourations*[Q] *seen in limbic zone of cornea*
- *Result from deposition of copper in Descemet's membrane*[Q] *of the cornea*
- *Do not interfere with vision*[Q]
- *Charachteristically seen in Wilson's disease*[Q] *but are not pathognomic*[Q] *of Wilson's disease* and may be seen in other conditions

| Conditions that may present with KF rings |
|---|
| • ***Wilson's disease (characteristic***[Q]***)*** |
| • *Chronic Active Hepatitis / Autoimmune Hepatitis* |
| • *Primary Biliary Cirrhosis* |
| • *Intrahepatic cholestatic syndromes* |

- *Present in almost all patients of Wilsons disease with Neurological /Psychiatric symptoms* (99% of patients)[Q]
- Present in only 30-50% of patients of Wilson's disease with only hepatic manifestations
- Absence of KF rings does not exclude the diagnosis of Wilson's disease[Q]
- May occasionally be visible to the naked eye without magnification but *definite diagnosis can only be made by an ophthalmologist using a slit lamp*[Q]

**200. Answer is C (Urinary copper excretion is <100µg/day):** *Harrison 18th/p 3188, 3189 Harrisons 17th/2450; Harrisons 16th/2313,2314*

***Urine copper is an important diagnostic too. Symptomatic patients invariably have urine copper levels > 100 µ (>1.6 umol) per 24 hours.***

**Wilson's disease is an autosomal recessive disorder**

*It is caused by a mutation of a gene on chromosome 13*[Q] *which promotes Cu excretion (ATP 7B gene)*

**Symptomatic patients with Wilson's disease invariably have urinary copper excretion of >100 µg per 24 hours (>1.6 µmol /24 hr)**

**Recommended Tests for Wilson's disease**

**Supportive Diagnostic Tests**

**Serum Ceruloplasmin levels**

| Normal | Wilson's Disease |
|---|---|
| 180-350mg/L (18-35 mg/dl) | Low in 90% |

Serum ceruloplasmin levels should not be used for definitive dagnosis because they are normal in upto 10% of affected patients

**Urinary copper Excretion /24 hours**

| Normal | Wilson's Disease |
|---|---|
| 20-50 µg (0.3-0.8 µmol/g) | Symptomatic pt >100 µg or >1.6 µ mol/g<br>Asymtomatic pt 60 to > 100 µg (0.9 ->1.6 µmol) |

Urine copper estimation is an important tool and a superior diagnostic tool for diagnosis of Wilson's disease in comparison to serum ceruloplasmin levels.

**KF Rings**

| Normal | Wilson's Disease |
|---|---|
| Absent | Present in 99% of patients with Neurological and psychiatric symptoms<br>Present in 30-50% of patients with hepatic presentation and presymptomatic state |

- KF rings can only be diagnosed definitely by an ophthalmologist using a slit lamp.
- The absence of KF rings does not exclude the diagnosis.

**Definitive Diagnostic test (Gold standard for diagnosis)**

**Liver Biopsy and quantitative copper Assays**

| Normal | Wilson's Disease |
|---|---|
| 20-50 µg (0.3-0.8 µmol/g) | > 200µg > 3.1 µmol/gm |

*Liver biopsy with quantitative copper assays is the gold standard investigation for the diagnosis of Wilson's disease*

Note that false positive results may be caused by long standing obstructive liver disease.

**Zinc is the treatment of choice for maintainance therapy in Wilson's disease**

Zinc is the treatment of choice in Wilson's disease for

- *Initial therapy in patients with hepatitis without decompensation*[Q]
- *Maintainance therapy*
- *Presymptomatic patient*
- *Pediatric patients*
- *Pregnant patients*

**201. Answer is A (Zinc):** *Harrison 18th/p 3188 Harrisons 17th/2451: Harrisons 16th/2313,2314*

*Presence of KF rings and decreased ceruloplasmin levels suggest the diagnosis of Wilson's disease.*
*The patient in question is presenting with intial hepatic disease without any evidence of hepatic decompensation.*
***Zinc is the therapy of choice for patients with hepatitis or cirrhosis without evidence of hepatic decompensation or neuropsychiatric symptoms.***

**Management of Wilson's disease**

- Wilson's disease with initial Hepatic manifestations (Hepatitis/cirrhosis)
  - Without evidence of Hepatic decompensation — *Zinc is the therapy of choice*
  - With evidence of hepatic decompensation — Chelater (Trientene preferred) along with zinc is the therapy of choice
- Wilson's disease with initial Neorological/Psychiatric Presentation — *Tetrathromolybdate is the drug of choice*

**202. Answer is C (Menke disease)**

***Menke's disease, also known as kinky hair disease, is an X-linked neurodegenerative disease of impaired copper transport, due to ATP 7A gene located on Xp12-13.*** *In Menkes disease, transport of dietary copper from intestinal cells is impaired, leading to the low serum copper levels*

**Inborn errors of Copper Metabolism**

*There are three inborn errors of Copper Metabolism; Wilson's Disease, Menke's Disease, and Occipital Horn Syndrome. Mutations in ATP7A lead to copper deficiency syndromes (Menkes' disease, Occipital horn syndrome) while mutations affecting ATP7B lead to copper overload syndrome (Wilson disease)*

| Inherited Condition | Gene | Presentation |
|---|---|---|
| *Wilson's Disease* | *ATP7B* | *Copper Overload Syndrome* |
| *Menke's Disease(Kinky Hair Disease)* | *ATP7A* | *Copper Deficiency Syndrome* |
| *Occipital Horn Syndrome (Ehlers Danlos-IX; Cutis Laxa)* | *ATP7A* | *Copper Deficiency Syndrome* |

## Hematochromatosis

**203. Answer is A (Hemochromatosis):** *Harrisons 16th/2288-2303; Harrisons 17th/2433 Harrison 18th/p 3164, 3165*

***The association of Arthritis, hyperpigmentation of skin and hypogonadism suggests the diagnosis of hematochromatosis.***

**Hematochromatosis (Disorder of iron storage)**

*Inappropriate increase in intestinal absorption results in deposition of excessive amounts of iron in parenchymal cells with eventual tissue damage and impaired function of organs*

*Serum iron ↑ed*
*% Transferrin saturation ↑ed*
*Serum ferritin ↑ed*
*Elevation in percent Transferrin saturation is the earliest phenotypic marker of herditary hemochromatosis*Q

| Liver | Skin | Pancreas | Joints | Heart | *Hypogonadism* |
|---|---|---|---|---|---|
| • Usually *first organ to be affected*<br>• Hepatomegaly is seen in 95% of symptomatic patients<br>• Cirrhosis may occur (Micronodular)<br>• Hepatocellular carcinoma (30% of patients with cirrhosis).<br>• It is the *most common cause of death in treated patients.* | • ***Excessive skin (Bronzing of skin) pigmentation*** is present in 90% of symptomatic patients<br>• Usually diffuse and generalized. May be more pronounced on Face, Neck, Extensor aspect of forearm, dorsa of hands, lower legs and genitalia and ears<br>• Usually results from increased melanin and iron in dermis | Involvement of pancreas *results in Diabetes mellitus* which is seen in 65% of symptomatic patients | • ***Arthropathy*** develops in 25-50% of patients<br>• *The joints of hands especially the 2nd and 3rd MCP joints are the first to be involved*<br>• Progressive polyarthritis involving wrist, knees, hips and ankles may also be seen | • Heart is involved in 15% of symptomatic patients<br>• The most common manifestation is congestive heart failure<br>• Cardiomyopathy and cardiac arrhythmias may be seen | • Results from impairment of Hypothalmo pituitary function by iron deposition which leads to decreased production of gonadotrophins |

### Treatment of Haematochromatosis

Therapy of Haematochromatosis involves removal of excessive body iron and supportive treatment of damaged organs

**Removal of Excessive Body iron**

- ***Phlebotomy is the treatment of choice***
  Iron removal is best accomplished by once or twice weekly phlebotomy of 500ml,
  - These should be continued until the serum ferritin level is < 50μg/L (May be required for 1-2 years)
  - Thereafter phlebotomies are performed at appropriate intervals to maintain ferritin levels between 50-100 μg/L (usually one phlebotomy every 3 months)
- **Chelating agents** *(such as Desferoxamine) are alternative agents and indicated when anemia and hypoproteinemia are severe enough to preclude phlebotomy*

*Alcohol consumption should be eleminated*Q *as it increases the risk of cirrhosis in hematochromatosis nearly ten fold.*

***The charachteristic clinical features of Haemochromatosis in order of frequency are*Q *:***

- *Hepatomegaly (95%)*
- *Skin pigmentation (90%)*
- *Diabetes mellitus (65%)*
- *Arthropathy (25-50%)*
- *Cardiac disease (15%)*
- *Hypogonadism*

**204. Answer is D (Eye):** *Harrison's 18th/ 3164; Refer Notes on Hemochromatosis*

*Ocular involvement in Hemochromatosis is unusual but may manifest as Limbal or Diffuse Conjunctival pigmentation*

*Liver is usually first organ to be affected and hepatomegaly is seen in 95% of symptomatic patients. Skin involvement (Bronzing of skin) is present in 90% of symptomatic patients. Joint involvement* ***(Arthropathy)*** develops in 25-50% of patients.

**205. Answer is C (Hemochromatosis):** *Refer Notes on Hemochromatosis; Harrison's 18th/ 3164, 3165*

***The association of Hepatic dysfunction (raised liver enzymes), Diabetes (Raised fasting Sugar), Skin pigmentation and Hypogonadism suggests a diagnosis of Hemochromatosis.***

*The Most Common Manifestation of Hemochromatosis is Hepatomegaly. Liver Enzymes may be normal or elevated depending on the extent of hepatocyte damage.*

**206. Answer is D (Increased Transferrin Saturation):** *Harrison 18th/p 3165, 3166; Mayo clinic Gastroenterology and Hepatology Board Review by Hauser 2nd/323; Clinical Laboratory medicine by Mc Clatchey 2nd/839*

*'A transferrin saturation of more than 45% is the earliest phenotypic abnormality in hereditary hematochromatosis'*
*- Hauser 2nd/3232*

***Transferrin saturation and measurement of unbound iron bindeng capacity are recommended for initial scrceening of individuals.***

**Tests Recommended for screening for Hereditary Hematochromatosis**

| Transferrin Saturation | Iron binding capacity (Unbound /Unsaturated) |
|---|---|
| • *A transferrin saturation of more than 45% is the earliest phenotypic abnormality in hereditary hematochromatosis*<br>• *Transferrin saturation is considered the best initial screening test for hereditary hematochromotosis*<br>• Transferrin saturation has a high sensitivity of >90% in diagnosing hereditary hematochromatosis<br>• Transferrin saturation is the ratio of serum iron to total iron binding capacity (SI/TIBC) | • *Unbound Iron binding capacity is an alternative screening test.*<br>• *Unbound Iron binding capacity UIBC=TIBC-Serum Iron*<br>• *Unbound iron binding capacity is decreased in hematochromatosis* |

**207. Answer is C (Increased Transferrin Saturation):** *Wintrobe's 12th/ 870; Conn's Current Therapy 2013: Expert Consult (Elsevier)/798; Harrison 18th*

***Transferrin Saturation is the first blood test to become elevated in Hemochromatosis.*** *The first biochemical manifestation of hemochromatosis is an increase of transferring saturation, which reflects an uncontrolled influx of iron into the blood stream from enterocytes and macrophages.*

*The serum transferrin saturation and serum ferritin levels are the two most important indicators of hemochromatosis and body iron stores. Elevation of transferrin levels precedes elevation of ferritin levels. The first biochemical manifestation of hemochromatosis is an increase in serum transferrin saturation. Serum iron concentration per se is not a good indicator for iron overload states like Hemochromatosis. Liver Enzymes may be normal or elevated depending on the extent of hepatocyte damage. They are usually normal or only mildly elevated in the early stages of hemochromatosis.*

**Laboratory findings in Hemochromatosis**

- Transferrin saturation is the first blood test to become elevated in hemochromatosis homozygotes

  The sensitivity of elevated transferring saturation to identify a patient with hemochromatosis is 94 to 98% and its specificity is 70 to 98%. Transferrin saturation is usually > 60% in symptomatic men and >50% in symptomatic women
- Unbound iron-binding capacity is usually decreased in homozygotes.
- Serum ferritin concentration is elevated in iron-loaded patients.
- Liver stainable iron and the hepatic iron index are also elevated in iron-loaded homozygotes.

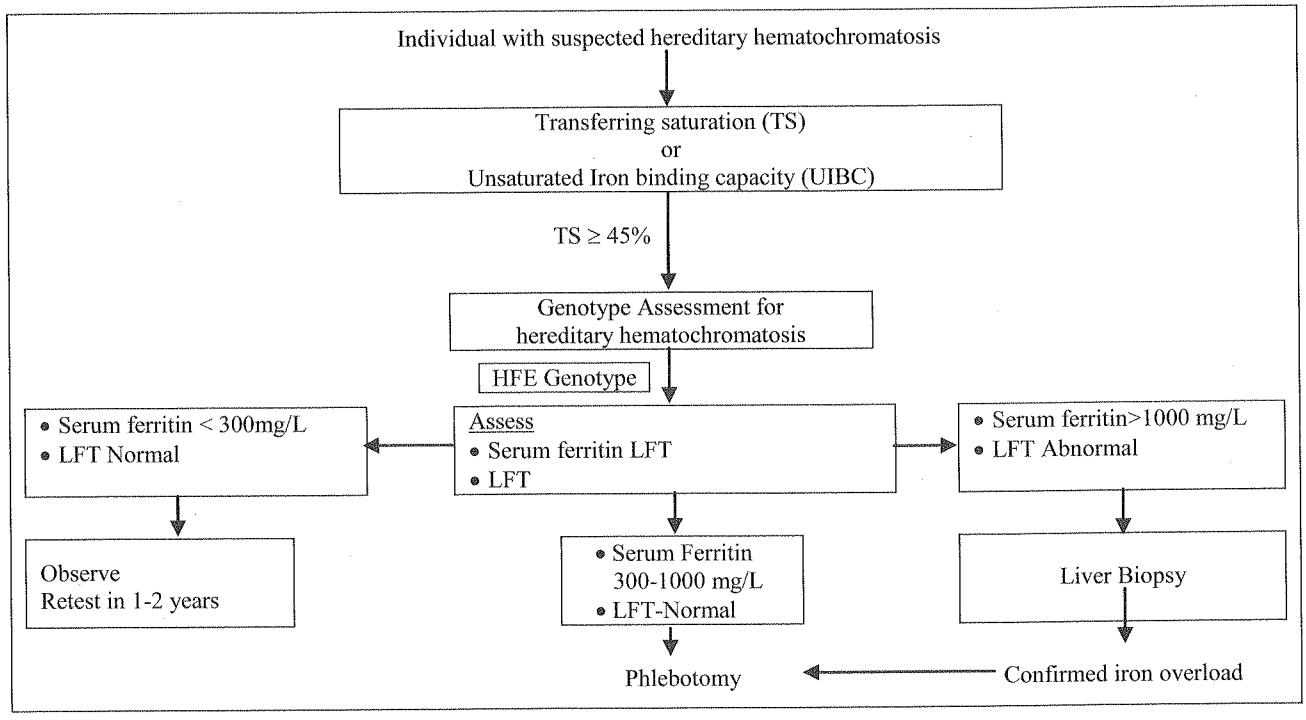
*DNA testing by polymerase chain reaction may be used to detect mutations of the HFE gene.*

**208. Answer is A (Iron binding capacity):** *Harrison 18th/p 3165, 3166 Harrisons 17th/2433*

*The presence of hyperpigmentation and diabetes (bronze diabetes) together with restrictive cardiomyopathy and cirrhosis suggests a diagnosis of hereditary hematochromatosis.*

*The best initial test to diagnose hereditary hematochromatosis are Transferrin saturation and unsaturated Iron binding capacity*

***As transferrin saturation is not provided amongst the options, Iron binding capacity is the single best answer of choice.***




**Note**

***Serum ferritin levels are a good index of body iron stores and are raised early during the cause of disease. Yet serum ferritin levels should not be used as initial screening test to detect hereditary hematochromatosis.***
***This is because serum ferritin also acts as an acute phase reactant and its levels are increased in variable infections and inflammatory conditions without iron overload. Also the serum concentration of ferritin may be increased in patients with hepatocellular injury as in viral hepatitis, alcoholic fatty liver disease or alcoholic liver diseases due to increased release from tissue cells.***

**209. Answer is C (MRI):** *Harrison 18th/ 1963; The Cleveland Clinic Cardiology Board Review Series 2nd/141; Oxford Textbook of Heart Failure (Oxford University Press) 2011/ 85*

***Cardiac MRI is the investigation of choice in Cardiomyopathy from Hemochromatosis.***

*Cardiac MRI helps distinguish amongst various causes of restrictive cardiomyopathy. Cardiac MRI in hemochromatosis allows non-invasive detection and quantification of myocardial iron load and distribution. Cardiac MRI is the imaging modality of choice as Echocardiography may be unable to distinguish hemochromatosis from dilated cardiomyopathy.*

**210. Answer is D (Desferrioxamine is the treatment of choice):** *Harrison 18th/3166; 17th/2433; Harrisons 16th/2288,2203*

***The treatment of choice for Hematochromatosis is removed of excess body iron by Phlebotomy and not with the use of chelating agents like desfernoxamine.***

**Phlebotomy is the treatment of choice in Hematochromatosis**

## Treatment of Haematochromatosis

Therapy of Haematochromatosis involves removal of excessive body iron and supportive treatment of damaged organs

**Removal of Excessive Body iron**

- ***Phlebotomy is the treatment of choice***
  Iron removal is best accomplished by once or twice weekly phlebotomy of 500ml,
  - These should be continued until the serum ferritin level is < 50μg/L (May be required for 1-2 years)
  - Thereafter phlebotomies are performed at appropriate intervals to maintain ferritin levels between 50-100 μg/L (usually one phlebotomy every 3 months)
- **Chelating agents** *(such as Desferoxamine) are alternative agents and indicated when anemia and hypoproteinemia are severe enough to preclude phlebotomy*

*Alcohol consumption should be eleminated[Q] as it increases the risk of cirrhosis in hematochromatosis nearly ten fold*

**Arthropathy, Hypogonadism, Diabetes and Bronzing (pigmentation) of skin are all characteristic manifestation of hematochromatosis**

***The charachteristic clinical features of Haemochromatosis in order of frequency are[Q] :***

- *Hepatomegaly (95%)*
- *Skin pigmentation (90%)*
- *Diabetes mellitus (65%)*
- *Arthropathy (25-50%)*
- *Cardiac disease (15%)*
- *Hypogonadism*

Note: The combination of skin hyperpigmentation and insulin deficiency (diabetes) is called Bronze diabetes.

## Miscellaneous

**211. Answer is B (7th):** *'Hepatology: Textbook and Atlas' (Springer, 2009) 3rd/ 153; Diseases of the Liver and Biliary System (John Wiley & Sons) 2008/38; Clinical and Surgical Anatomy by Singh 2nd/170*

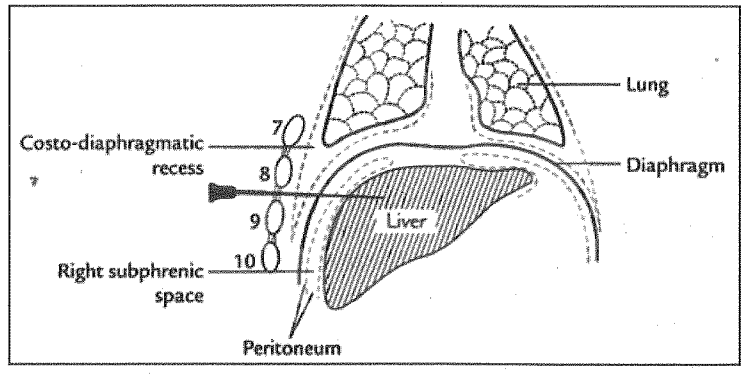
***Typically the uppermost intercostal space utilized for Hepatic Biopsy is 6th or 7th intercostal space.***

*The right surface of the liver is in contact with the diaphragm opposite the 7th to 11th ribs. In needle biopsy of the liver through the intercostal route, the needle may be inserted through the 6th 7th, 8th, 9th or 10th right intercostal space in the mid-axillary line. The 8th and 9th intercostal spaces are most commonly used. Insertion in the 6th or 7th intercostal space may also be used but is associated with risk of injury to the Lung. Needle is typically inserted at the end of expiration (Attempted Apnoea).*

**212. Answer is D (8th):** *Clinical and Surgical Anatomy by Singh 2nd/ 170; 'Hepatology: Textbook and Atlas' (Springer, 2009) 3rd/ 153; Diseases of the Liver and Biliary System (John Wiley & Sons) 2008/38; Clinical and Surgical Anatomy by Singh 2nd/ 170*

***The 8th and 9th intercostal spaces are most commonly used intercostal spaces for hepatic biopsy.***

- *The right surface of the liver is in contact with the diaphragm opposite the 7th to 11th ribs.*
- *In needle biopsy of the liver through the intercostal route, the needle may be inserted through the 6th 7th, 8th, 9th or 10th right intercostal space in the mid-axillary line.*
- ***The 8th and 9th intercostal spaces are most commonly used.***
- *Insertion in the6th or 7th intercostal space may also be used but is associated with risk of injury to the Lung.*
- *Needle is typically inserted at the end of expiration (Attempted Apnoea).*



**213. Answer is D (Liver biospsy):** Hepatology: Textbook and Atlas 3rd/150 ; Atlas of Clinical Hematology 4th/7 *CMDT 2014/665*

***Menghini's needle is primarily used for percutaneous Liver Biopsy. This needle may also be used for percutaneous biopsy of the spleen***

**214. Answer is C (Glutathione-S- Transferase is used as a hepatic prognostic marker after surgery):** *Harrison's 18th/2528; Schiff Diseases of the Liver 11th/chapter 2; Biomarkers of Disease. An Evidence Based Approach (Cambridge University Press) 2006/169*

***Glutathione – S – Transferase is an emerging enzyme marker for post-transplant monitoring (surgery) as an aid to the diagnosis of acute allagraft rejection***

*ALT is a more specific indicator of liver injury than AST and absolute levels of aminotransferase do not correlate with outcome.*

**ALT is a more specific indicator of Liver injury than AST**

*'AST (Aspartate Aminotransferase) is found in the liver, cardiac muscle, skeletal muscle, kidneys, brain, pancreas, lung, leukocytes and erythrocytes in decreasing order of concentration.*
***ALT is found primarily in the liver and is therefore a more specific indicator of Liver injury*** *- Harrison's 18th/2528*

**Absolute level of Aminotransferase elevation do not correlate with outcome**

*'There is poor correlatation between extent of Liver cell Necrosis and the elevation of serum aminotransferase levels in chronic liver diseases. Similarly, absolute elevation of aminotransferase levels is of little value in predicting the outcome of acute hepatocellular disorders' - Schiff's Deseases of the Liver*

**Serum Glutathione – S- Transferase may be used as a prognostic marker after transplant surgery**

*'Serum Alpha – Glutathione – S – Transferase is an emerging static test indicating hepatocellular damage. As in vivo plasma half life of this enzyme is less than 60-90 minutes, this enzyme offer advantages in post-transplant monitoring as an aid to the diagnosis of acute allagraft rejection. Recent investigations have indicated that monitoring of GST reduced both mortality and morbidity in liver transplant recipients. GST showed a distinct higher sensitivity (81%) for acute rejection than conventional liver function tests (the specificity however was relatively low (45%).*
*- Biomarkers of Disease: Evidence Based Approach*

**Glutathione – S-Transferase (GST)** - *Miller's Anesthesia (Elsevier) 2010/426*
*Glutathione-S-Transferase is a sensitive and specific test for some patterns of Liver injury. The enzyme has a brief plasma half life (90 minutes) and is released rapidly into circulation following hpatocellular injury. Thus serial GST measurements can reveal time course of hepatic injury from its onset to its resolution. In contrast to AST and ALT which reside in Acinar Zone I, GST localizes in Acinar Zone III (centrilobular region). This zone contains the hepatacyte population with highest susceptibility to injury from hypoxia or reactive drug metabolites. Accordingly GST would be more sensitive than AST or ALT as a marker of contrilobular necrosis in its incipient stage.*

**215. Answer is A (Bulky Disease):** *Essentials of Clinical Oncology (Jaypee)2005/324; Principles & Practice of Surgical Oncology (Lippincott Williams) 2009/964*

***The most important role of serum LDH is to estimate the tumor bulk (volume of tumor).***

*'LDH levels are elevated in large volume bulky tumors of any histology. LDH levels when elevated correlate well with the volume of tumor' – The Essential of clinical oncology.*

*'LDH elevation provides a useful guide to bulk of disease; Bulky Disease (In Hodgkin's Lymphoma) is a node mass more than 10 cm in diameter' - 'Essential Revision notes for MRCP' by Katra (PasTest)2004/288*
*Serum LDH is a non specific marker elevated in a variety of tumors.*

**216. Answer is A (5% weight loss in 1-2 months):** *Medical Nutrition & Disease:A case based approach (John Wiley & Sons)2009/10*

***Significant weight loss is defined as 5% weight loss in 1 month.***

**Percent weight change over a period of time** is calculated using the person's current body weight and person's usual body weight.

$$\text{Percent weight change} = \frac{\text{Usual weight} - \text{Current weight}}{\text{Usual weight}}$$

**Severity of weight loss is thereby defined by percent change in a defined period of time**

| Time | Significant weight | Severe weight loss |
|---|---|---|
| 1 week | *1-2%* | *>2%* |
| 1 month | *5%* | *>5%* |
| 3 months | *7.5%* | *7.5%* |
| 6 months | *10%* | *10%* |
| 1 year | *20%* | *20%* |

**217. Answer is A (Liver transplantation)**

***The Milan criteria are currently used to define acceptable candidates for liver transplantation***

In transplantation medicine, the Milan criteria are applied as a basis for selecting patient with cirrhosis and hepatocellular carcinoma for liver transplantation. The **Milan criteria are used** to define a pretransplant threshold that predicts acceptable posttransplant HCC recurrence rates.

Milan Criteria are the most widely used criteria for liver transplantation
(UCSF Criteria -University of California, San Fransisco- Criteria have been proposed and are comparable to Milan Criteria)

**218. Answer is D (Serum albumin):** *CMDT 2014/692*

***The Model for End-Stage Liver Disease, or MELD Score is based on three variables that include INR, bilirubin and creatinine.***

The **Model for End-Stage Liver Disease**, or **MELD**, *is a scoring system for assessing the severity of chronic liver disease. The original score is based on three variables that include INR, bilirubin and creatinine*

| Essential Variables For The Original MELD Score |
|---|
| • **INR** |
| • **Creatinine** |
| • **Bilirubin** |

The Model for End-Stage Liver Disease (MELD) is a reliable measure of mortality risk in patients with end-stage liver disease. It is to help prioritize allocation of organs for transplant.

| MELD Score along with it several modifications has been used for |
|---|
| • Survival probability of a patient with end stage liver disease |
| • Predict 90 Days/three month mortality of surgery in patients who have undergone a transjugular intrahepatic portosystemic shunt (TIPS) procedure. |
| • Predict 90 Days/three month mortality from alcoholic hepatitis |
| • As a disease severity index for prioritizing allocation of a liver transplant. This score is now also used at various centers for prioritizing allocation of liver transplants instead of the older Child-Pugh score |

**219. Answer is A (Alcoholic hepatitis):** *API Textbook of Medicine 9th/ 853*

***Maddrey discriminant score is used for determining severity of Alcoholic Hepatitis and predict mortality.*** .

*Acute hepatitis (AH) in patients with chronic alcoholic liver disease is associated with high mortality. It is therefore vital to identify patients at greatest risk of mortality who may benefit from aggressive intervention and steroid therapy. The Maddrey's Discriminant Function relies on two factors (prothrombin time and serum bilirubin) and suggests which patients with alcoholic hepatitis (Score > 32) may have a poor prognosis and are likely to benefit from steroid administration.*

**220. Answer is All (All of the above) :** *CDT in Gastroenterology, Hepatology and Endoscopy (2009)/518, Harrison's 17th/1984*

***Biliary atresia is an indication for Liver transplantation in children while primary Biliary Cirrhosis, Sclerosing cholangitis and Hematochromatosis an established indications for Liver transplantation in adults***

**Indication for Liver Transplantation:**

| Children | Aduts |
|---|---|
| Biliary atresia | Primary biliary cirrhosis |
| Neonatal hepatitis | Secondary biliary cirrhosis |
| Congenital hepatic fibrosis | Primary sclerosing cholangitis |
| Alagille's disease[a] | Autoimmune hepatitis |
| Byler's disease[b] | Caroli's disease[c] |
| α1-Antitrypsin deficiency | Cryptogenic cirrhosis |
| Inherited disorders of metabolism | Chronic hepatitis with cirrhosis |
| Wilson's disease | Hepatic vein thrombosis |
| Tyrosinemia | Fulminant hepatitis |
| Glycogen storage diseases | Alcoholic cirrhosis |
| Lysosomal storage diseases | Chronic viral hepatitis |
| Protoporphyria | Primary hepatocellular malignancies |
| Crigler-Najjar disease type 1 | Hepatic adenomas |
| Familial hypercholesterolemia | Nonalcoholic steatohepatitis |
| Primary hyperoxaluria type 1 | Familial amyloid polyneuropathy |
| Hemophilia | |

[a]Arteriohepatic dysplasia, with paucity of bile ducts, and congenital malformations, including pulmonary stenosis.
[b]Intrahepatic cholestasis, progressive liver failure, mental and growth retardation
[c]Multiple cystic dilatations of the intrahepatic biliary tree.

**Hematochromatosis is also an indication for Liver Transplantation**

*'Among genetic and metabolic conditions, Hematachroatosis is the most common reason for Liver Transplantation'* - *Current Gastroenterology & Hepatology (LANGE) 2009/518*

**221. Answer is D (Estimation of Galactose Elimination capacity):** *'Textbook of Hepatology' by Rodes 3rd / 475*

***Estimation of Galactose Elimination capacity (GEC) is an example of quantitative liver tests***

Liver Function tests

| Non quantitative Tests for Liver Function | Quantitative tests for Liver Function |
|---|---|
| Although generally termed as Liver function tests, these are either not related to function or only reflect given aspects of liver function and are not over all parameters of latter | Quantitative tests for Liver function measure the true functional reserve of the liver |
| These Include | These Include |
| • *Serum Bilirubin*<br>• *Serum Alkaline phosphatase*<br>• *Serum Transminases*<br>• *Serum Bile Acids*<br>• *Serum Albumin*<br>• *Serum prothrombin time, etc* | • ***Galactose Elimination capacity***<br>• *Urea synthesis capacity*<br>• *Inducyanine clearance*<br>• *Sorbitol clearance*<br>• *Caffeine clearance*<br>• *Aminopyrine Breath test*<br>• *Ketoisocaproic acid breath test* |

**222. Answer is D (Hepatic Porphyrias):** *Harrison's 16th/2316,2320; Oxford Textbook of Medicine 4th/69, Gastrointestinal and Liver Disease by Feldman 8th/1623*

***Frank Hepatomegaly is rare in hepatic porphyrias***

*Although hepatomegaly may occasionally be seen in hepatic porphyrias, frank hepatomegaly is rare and not a prominent manifestation of hepatic porphyria .Hepatic porphyria is therefore the single best answer by exclusion*

**Frank signs of hepatomegaly are rare in Hepatic Porphyrias but have been noted.**

Hepatic involvement in porphyria is variable

Patients with *acute hepatic porphyria* generally have elevation of serum aminotransferases and bile acid levels.
Patients with *chronic hepatic porphyrias* (porphyria cutanea tarda) may show liver enlargement with fatty infiltration
***but frank signs of hepatomegaly and iron overload are rare***

**Hepatomegaly is a prominent manifestation of Hurler's syndrome, Nieman Pick disease and Von Girke's Disease**
*(Harrison's 16th/2316,2320)*

| *Condition* | | *Hepatomegaly* |
|---|---|---|
| *Hurler's syndrome* | (Mucopolysacharidosis) | Prominent |
| *Nieman Pick Disease* | (Glycosphingolipidosis) | Prominent |
| *Von Girke's Disease* | (Hepatic Glycogen Storage Disease) | Prominent |

**223. Answer is D (Albumin):** *Harrisons 16th/ 1815*

***Only minimal changes in serum albumin are seen in acute liver conditions. Hypoalbuminemia is common in chronic liver disorders such as cirrhosis. In hepatitis serum albumin levels of less than 3g/dl (hypoalbuminemia) should raise the possibility of chronic liver disease'*** *– Harrisons 16th/ 1815*

**Albumin as marker for liver dysfunction**

- Serum albumin is synthesized exclusively by hepatocytes
- Serum albumin has a long half life and is degraded very slowly (approx 4% is degraded per day.)
  Because of this slow turnover, the serum albumin is not a good indicator of acute hepatic dysfunction.
- Acute liver conditions are associated with only minimal changes in serum albumin (Albumin levels may be normal or minimally altered in viral hepatitis drug related hepato-toxity and obstructive jaundice)
- Chronic liver conditions are associated with hypoalbuminemia reflecting decreased albumin synthesis from severe and prolonged liver dysfunction.

*Remember: Hypoalbuminemia is not specific for liver disease and may occur in protein malnutrition of any cause, protein losing enteropathies nephritic syndrome and chronic infections.*

- **Aminotransferases** are used as indicators of extent of hepatocellular injury. They may be elevated in both acute and chronic hepatocellular disorders.
- **Alkaline phosphatase** is an enzyme used as markers of cholestasis and again may be elevated in both acute and chronic cholestatic disorders.
- **Bilirubin** levels also may be elevated in both acute and chronic liver disease.

**224. Answer is B (Sclerosing Cholangitis):** *Sutton 7/e P-714; Grainger 4/e P-984; CSDT 2003-600*

***Sclerosing cholangitis is not associated with air in the biliary tract.***

**Causes of air in biliary tract**

| Air coming from GI tract through fistulas caused by | Air Produced with in Biliary tract | Air coming from GI tract d/t failure of closure of sphincter of oddi l/t reflux of duodenal gas |
|---|---|---|
| • Trauma<br>• Surgery<br>• ***Malignancy***$^{Q}$<br>• Duodenal Ulcer<br>• ***Gall stone ileus***$^{Q}$ | • *Emphysematous cholecystitis*$^{Q}$ | • Passage of Stone<br>• Passage of Ascaris (Biliary ascariasis)<br>• Surgery (endoscopic sphincterotomy, sphincteroplasty, ***papillotomy***) |

**225. Answer is A (Albendazole):** *Harrison 18th /1763; Goodman Gillman 11th/710*

*The drug of choice for treatment of Echinococcus granulosus infection (Hydatid cyst) is* ***Albendazole.***

**226. Answer is E (Chlorpromazine):** *CMDT 2008 / 582; Harrisons 17th*

***Chlorpromazine is associated with inflammatory cholestasis and not with Bland (non inflammatory) cholestasis.***

Cholestatic Reactions

| Non Inflammatory (Bland) | Inflammatory |
|---|---|
| *Bland cholestasis is characterized by cholestasis in the absence of inflammation (hepatitis). This is believed to result from inhibition of various hepatobiliary transport systems.* | *Inflammatory cholestasis is charachterized by inflammation of portal tracts with bile duct injury often associated with allergic features like eosinophilia* |
| Important Drugs causes Bland cholestasis<br>• *Estrogen and OCP*<br>• *Anabolic steroids and / or 17 α substituted androgens*<br>• *Indinavir*<br>• *Mercaptopurine*<br>• *Methyl testesterone*<br>• *Cyclosporine* | Important drugs causing inflammatory cholestasis<br>• *Amoxiciline – Clavulanic acid*<br>• *Azathioprine*<br>• *Captopril*<br>• *Chlorthiazide*<br>• *Chlorpropamide*<br>• *Pencillamine*<br>• *Semisynthetic pencillins*<br>• *Azithromycin*<br>• *Cephalosporins*<br>• *Chlorpromazine*<br>• *Erythromycin*<br>• *Prochlorperazine*<br>• *Sulphadiazine* |

# NOTES